(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)



(19) World Intellectual Property Organization International Bureau



(43) International Publication Date 29 November 2001 (29.11.2001)

PCT

(10) International Publication Number WO 01/90304 A2

- (51) International Patent Classification?:
- ____
- (21) International Application Number: PCT/US01/16450
- (22) International Filing Date: 18 May 2001 (18.05.2001)
- (25) Filing Language:

English

C12N

(26) Publication Language:

English

(30) Priority Data: 60/205,515

19 May 2000 (19.05.2000) U

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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- without international search report and to be republished upon receipt of that report
- with sequence listing part of description published separately in electronic form and available upon request from the International Bureau

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

A2

(54) Title: NUCLEIC ACIDS, PROTEINS, AND ANTIBODIES

(57) Abstract: The present invention relates to novel proteins. More specifically, isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to these novel polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

WO.01/90304

Nucleic Acids, Proteins, and Antibodies

This application refers to a "Sequence Listing" that is provided on electronic media in computer readable form pursuant to Administrative Instructions Section 801(a)(i) and as a paper copy. The Sequence Listing forms a part of this description pursuant to Rule 5.2 and Administrative Instructions Sections 801 to 806, and is hereby incorporated in its entirety.

The Sequence Listing is provided as an electronic file (PA131PCTSL..txt, 5,210,863 bytes in size, created on May 18, 2001) on three identical compact discs (CD-R), labeled "COPY 1," "COPY 2," and "CRF." The Sequence Listing complies with Annex C of the Administrative Instructions, and may be viewed, for example, on an IBM-PC machine running the MS-Windows operating system by using the V viewer software, version 2000 (see World Wide Web URL: http://www.fileviewer.com).

Field of the Invention

[0001] The present invention relates to novel proteins. More specifically, isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to these novel polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

Background of the Invention

[0002] Protein transport is a quintessential process for both prokaryotic and eukaryotic cells. Transport of an individual protein usually occurs via an amino-terminal signal sequence, which directs, or targets, the protein from its ribosomal assembly site to a particular cellular or extracellular location. Transport may involve any combination of several of the following steps: contact with a chaperone, unfolding, interaction with a receptor and/or a pore complex, addition of energy, and refolding. Moreover, an

extracellular protein may be produced as an inactive precursor. Once the precursor has been exported, removal of the signal sequence by a signal peptidase activates the protein.

Although amino-terminal signal sequences vary substantially, many patterns [0003] and overall properties are shared. Recently, hidden Markov models (HMMs), statistical alternatives to FASTA and Smith Waterman algorithms, have been used to find shared patterns, specifically consensus sequences (Pearson, W.R. and D.J. Lipman PNAS 85:2444-48 (1988); Smith, T.F. and M.S. Waterman J. Mol. Biol. 147:195-97 (1981)). Although they were initially developed to examine speech recognition patterns, HMMs have been used in biology to analyze protein and DNA sequences and to model protein structure (Krogh, A. et al. J. Mol. Biol. 235:1501-31 (1994); Collin, M. et al. Protein Sci. 2:305-14 (1993)). HMMs have a formal probabilistic basis and use position-specific scores for amino acids or nucleotides and for opening and extending an insertion or deletion. The algorithms are quite flexible in that they incorporate information from newly identified sequences to build even more successful patterns. Other methods exist to identify membrane associated proteins. Klein et al. have developed a method ("ALOM", also called as KKD) to detect potential transmembrane segments in polypeptides (Klein, P. et al. Biochim. Biophys. Acta, 815:468 (1985)). It attempts to identify the most probable transmembrane segment from the average hydrophobicity value over a range of amino acid residues. It predicts whether the segment is a transmembrane segment (INTEGRAL) or not (PERIPHERAL) and thus, can suggest membrane association of a polypeptide.

[0004] Some examples of the protein families which are known to be plasma membrane associated are receptors (nuclear, 4 transmembrane, G protein coupled, and tyrosine kinase), cytokines (chemokines), hormones (growth and differentiation factors), neuropeptides and vasomediators, protein kinases, phosphatases, phospholipases, phosphodiesterases, nucleotide cyclases, matrix molecules (adhesion, cadherin, extracellular matrix molecules, integrin, and selectin), seven transmembrane receptors, ion channels (calcium, chloride, potassium, and sodium), proteases, transporter/pumps (amino acid, protein, sugar, metal and vitamin; calcium, phosphate, potassium, and sodium) and regulatory proteins. Descriptions of some of these proteins (seven transmembrane receptors, kinases, matrix proteins, fibronectins, defensins, EF-hand domain containing

proteins, mac/perforin family members, pancreatic hormones, serine carboxypeptidases, tumor necrosis factors (TNFs)) and diseases associated with their dysfunction follow.

Seven transmembrane receptors-

[0005] The seven transmembrane receptors (also known as heptahelical, serpentine, or G protein-coupled receptors) comprise a superfamily of structurally related molecules. Possible relationships among seven transmembrane receptors (7TM receptors) for which amino acid sequence had previously been reported are reviewed in Probst et al., DNA and Cell Biology, 11(1):1-20 (1992). Briefly, the 7TM receptors exhibit detectable amino acid sequence similarity and all appear to share a number of structural characteristics including: an extracellular amino terminus; seven predominantly hydrophobic α -helical domains (of about 20-30 amino acids) which are believed to span the cell membrane and are referred to as transmembrane domains TM 1-7; approximately twenty well-conserved amino acids; and a cytoplasmic carboxy terminus.

[0006] Each 7TM receptor is predicted to associate with a particular G protein at the intracellular surface of the plasma membrane. The binding of the receptor to its ligand is thought to result in activation (i.e., the exchange of GTP for GDP on the α-subunit) of the G protein which in turn stimulates specific intracellular signal-transducing enzymes and channels. Thus, the function of each 7TM receptor is to discriminate its specific ligand from the complex extracellular milieu and then to activate G proteins to produce a specific intracellular signal. Transmembrane domain-3 (TM3) is believed to be essential in signal transduction (Cotecchia et al., *Proc. Natl. Acad. Sci.*, USA, 87:2896-2900 (1990)). Other regions may be essential for biological activity as well (Lefkowitz, *Nature*, 265:603-604 (1993)).

[0007] Mutations in the third intracellular loop of one 7TM receptor (the thyrotropin receptor) and in the adjacent sixth transmembrane domain of another 7TM receptor (the luteinizing hormone receptor) have been reported to be the genetic defects responsible for an uncommon form of hyperthyroidism (Parma et al., Nature, 365:649-651 (1993) and for familial precocious puberty (Shenker et al., Nature, 365:652-654 (1993)), respectively. In both cases the mutations result in constitutive activation of the G protein receptors. Other studies have shown that mutations that prevent the activation of 7TM receptors are responsible for states of hormone resistance which are responsible for diseases such as

congenital nephrogenic diabetes insipidus. See Rosenthal et al., J. Biol. Chem., 268:13030-13033 (1993). Still other studies have shown that several 7TM receptors can function as protooncogenes and be activated by mutational alteration. See, for example, Allen et al., Proc. Natl. Acad. Sci. USA, 88:11354-11358 (1991) which suggests that spontaneously occurring mutations in some 7TM receptors may alter the normal function of the receptors and result in uncontrolled cell growth associated with human disease states such as neoplasia and atherosclerosis. Therefore, mutations in 7TM receptors may underlie a number of human pathologies.

Kinases-

[0008] The kinases comprise the largest known group of proteins, a superfamily of enzymes with widely varied functions and specificities. Kinases regulate many different cell proliferation, differentiation, and signaling processes by adding phosphate groups to proteins. Receptor mediated extracellular events trigger the transfer of these high energy phosphate groups and activate intracellular signaling cascades. Activation is roughly analogous to the turning on a molecular switch, and in cases where signalling is uncontrolled, may be associated with or produce inflammation and cancer.

[0009] Almost all kinases contain a similar 250-300 amino acid catalytic domain. The N-terminal domain, which contains subdomains I-IV, generally folds into a two-lobed structure which binds and orients the ATP (or GTP) donor molecule. The larger C terminal lobe, which contains subdomains VIA-XI, binds the protein substrate and carries out the transfer of the gamma phosphate from ATP to the hydroxyl group of a serine, threonine, or tyrosine residue. Subdomain V spans the two lobes.

[0010] The kinases may be categorized into families by the different amino acid sequences (between 5 and 100 residues) located on either side of, or inserted into loops of, the kinase domain. These amino acid sequences allow the regulation of each kinase as it recognizes and interacts with its target protein. The primary structure of the kinase domain is conserved and contains specific residues and identifiable motifs or patterns of amino acids. The serine threonine kinases represent one family which preferentially phosphorylates serine or threonine residues. Many serine threonine kinases, including those from human, rabbit, rat, mouse, and chicken cells and tissues, have been described

(Hardie, G. and Hanks, S. (1995) The Protein Kinase Facts Books, Vol 1:7-20 Academic Press, San Diego, CA).

Matrix Proteins-

[0011] The matrix proteins (MPs) provide structural support, cell and tissue identity, and autocrine, paracrine and juxtacrine properties for most eukaryotic cells (McGowan, S.E. (1992) FASEB J. 6:2895-2904). MPs include adhesion molecules, integrins and selectins, cadherins, lectins, lipocalins, and extracellular matrix proteins (ECMs). MPs possess many different domains which interact with soluble, extracellular molecules. These domains include collagen-like domains, EGF-like domains, immunoglobulin-like domains, fibronectin-like domains, type A domain of von Willebrand factor (vWFA)-like modules, ankyrin repeat modules, RDG or RDG-like sequences, carbohydrate-binding domains, and calcium-binding domains.

[0012] The diversity, distribution and biochemistry of MPs is indicative of their many, overlapping roles in cell proliferation and cell signaling. MPs function in the formation, growth, remodeling, and maintenance of bone, and in the mediation and regulation of inflammation. Biochemical changes that result from congenital, epigenetic, or infectious diseases affect the expression and balance of MPs. This balance, in turn, affects the activation, proliferation, differentiation, and migration of leukocytes and determines whether the immune response is appropriate or self-destructive (Roman, J. (1996) Immunol. Res. 15:163-178).

Fibronectins-

[0013] Fibronectin proteins play a vital role in the structure and function of the extracellular matrix (ECM). Defects in the function of the ECM are thought to be involved in diseases such as osteoporosis, atherosclerosis, arthritis, and fibrotic diseases. Fibronectin enables cells to adhere to the ECM, and influences the growth and migration of cells as well as the organization of the cytoskeleton. As a major component of the ECM, Fibronectin is thought to influence such processes as cellular adhesion and migration, particularly during development, as well as processes such as wound repair (R.O. Hynes, *PNAS*, 96:2588-90 (1999)).

[0014] Fibronectin is a disulfide-linked dimeric glycoprotein composed of type I, type II, and type III fibronectin repeats. Type I repeats are approximately 45 amino acids in length and are located at the amino- and carboxy-termini of the protein. Type II domains are approximately 40-60 amino acids in length, and contain four conserved cysteines involved in disulfide bonding. It is thought that the type II domains may function in collagen binding. There are approximately 15-17 type III domains, arranged in tandem in the middle of the protein, that are thought to provide elasticity to fibronectin.

Defensins-

[0015] Mammalian defensins are produced by the epidermis and mucosal epithelium as innate effector molecules thought to function in an antimicrobial capacity. Defensins are cytotoxic peptides with a broad range of activity on gram-positive and negative bacteria, fungi, parasites, viruses, and mycobacteria. The two characterized defensins are the alpha and beta defensins. The alpha-defensins are produced by neutrophils and macrophage, while the beta-defensins are produced by epithelia (Singh, P.K., et al., PNAS, 95:14961-66 (1998); Lillard, J.W., et al., PNAS, 96:651-56 (1999)).

[0016] Defensin peptides range in length from approximately 29 to 35 amino acids, and include six conserved cysteine residues involved in disulfide bond formation and protein folding. The distribution and connection of the cysteine residues differs between the alpha and beta defensins.

EF-hand domain containing proteins-

[0017] Calcium is well known to be essential for cell signaling. However, calcium also plays a role in such cellular processes as protein processing and membrane traffic to and through the Golgi. Many proteins thought to be involved in the binding of calcium accomplish this in part through a protein calcium-binding domain known as the EF-hand domain.

[0018] The domain consists of a twelve residue loop flanked by a twelve residue alphahelical domain on both sides. In the EF hand loop, the calcium ion is situated in a coordinated pentagonal bipyramidal configuration. An invariant Glutamic acid or Aspartic acid residue provides two oxygens for liganding the calcium ion.

[0019] Proteins containing this domain include aequorin and Renilla luciferin binding protein (LBP), Recoverins, Calmodulin, Calpain small and large chains, Calretinin, Calcyclin, Fimbrin, Serine/Threonine protein phosphatase, and Diacylglycerol kinase, for example.

MAC/Perforin Family Members-

[0020] The Membrane Attack Complex (MAC) is one of the sequentially activated, membrane bound complexes of the complement system used to eliminate diseased or non-compliant cells. Under this system, activated C5b sequentially binds C6 and C7, which insert into cell membranes. This complex then binds one molecule of C8, followed by between 1 and 18 molecules of C9, which polymerizes to generate a transmembrane channel. These transmembrane channels pierce the membrane, increasing the cell's permeability. These channels permit small molecules in the cell to exchange with the medium. Therefore, water is osmotically drawn into the cell, eventually resulting in the cell bursting.

[0021] Similarly, Perforin is a molecule produced by cytotoxic T cells. In the presence of calcium, Perforin polymerizes into transmembrane channels capable of lysing a variety of target cells in a nonspecific manner.

Pancreatic Hormones-Serine Carboxypeptidases-

[0022] Pancreatic hormone (PP) is a peptide of approximately 80 amino acids in length that is generated in pancreatic islets of Langherhans and consequently secreted. Pancreatic hormone is thought to function as a regulator of pancreatic and gastrointestinal functions.

[0023] Representative members of the pancreatic hormones family of proteins include Neuropeptide Y, Peptide YY, and skin peptide YY. These proteins may be useful as therapeutics for controlling secretion of the gonadotropin-releasing hormone, disorders related to feeding, vasoconstrictory actions, and colonic mobility, as well as antibacterial and antifungal activity.

Serine Carboxypeptidases-

[0024] Carboxypeptidases catalyze the hydrolysis of C-terminal residues of polypeptides. Carboxypeptidases are identified either as metallo-carboxypeptidases or serine-carboxypeptidases.

[0025] Serine carboxypeptidases have the ability to hydrolyze peptides as well as peptide amides from the C-terminus, and have a preferential release of a C-terminal arginine or lysine residue. Their subcellular location is usually extracellular or intracellular. The catalytic activity of serine carboxypeptidases is provided by a charge relay system involving an aspartic acid residue hydrogen-bonded to a histidine, which is itself hydrogen bonded to a serine.

Tumor necrosis factors (TNF)-

Tumor necrosis factors (TNF) alpha and beta are cytokines, which act through TNF receptors to regulate numerous biological processes, including protection against infection and induction of shock and inflammatory disease. The TNF molecules belong to the "TNF-ligand" superfamily, and act together with their receptors or counterligands, the "TNF-receptor" superfamily. So far, nine members of the TNF ligand superfamily have been identified and ten members of the TNF-receptor superfamily have been characterized.

[0027] Many members of the TNF-ligand superfamily are expressed by activated T-cells, implying that they are necessary for T-cell interactions with other cell types which underlie cell ontogeny and functions (Meager, A., supra).

[0028] Considerable insight into the essential functions of several members of the TNF receptor family has been gained from the identification and creation of mutants that abolish the expression of these proteins. For example, naturally occurring mutations in the FAS antigen and its ligand cause lymphoproliferative disease (Watanabe-Fukunaga, R. et al., Nature 356:314 (1992)), perhaps reflecting a failure of programmed cell death. Mutations of the CD40 ligand cause an X-linked immunodeficiency state characterized by high levels of immunoglobulin M and low levels of immunoglobulin G in plasma, indicating faulty T-cell-dependent B-cell activation (Allen, R.C. et al., Science 259:990 (1993)). Targeted mutations of the low affinity nerve growth factor receptor cause a disorder characterized by faulty sensory innovation of peripheral structures (Lee, K.F. et al., Cell 69:737 (1992)).

[0029] TNF and LT-α are capable of binding to two TNF receptors (the 55- and 75-kd TNF receptors). A large number of biological effects elicited by TNF and LT-α, acting through their receptors, include hemorrhagic necrosis of transplanted tumors, cytotoxicity, a role in endotoxic shock, inflammation, immunoregulation, proliferation and anti-viral responses, as well as protection against the deleterious effects of ionizing radiation. TNF and LT-α are involved in the pathogenesis of a wide range of diseases, including endotoxic shock, cerebral malaria, tumors, autoimmune disease, AIDS and graft-host rejection (Beutler, B. and Von Huffel, C., Science 264:667-668 (1994)). Mutations in the p55 Receptor cause increased susceptibility to microbial infection.

[0030] Moreover, an about 80 amino acid domain near the C-terminus of TNFR1 (p55) and Fas was reported as the "death domain," which is responsible for transducing signals for programmed cell death (Tartaglia et al., Cell 74:845 (1993)).

[0031] Plasma membrane associated proteins with a predominant tissue expression pattern are important targets for targeted drug delivery, tumor-targeted therapy (e.g., including, but not limited to, radioimmunotherapy) antibody mediated attack of diseased tissues or cancers, and immune mediated cytotoxicity.

[0032] The discovery of new plasma membrane associated proteins and the polynucleotides encoding these molecules thus satisfies a need in the art by not only providing new compositions useful in the diagnosis, treatment, and prevention of diseases associated with cell proliferation and cell signaling, particularly cancer, immune response and neuronal disorders; but also by providing new targets for immune based therapies.

Summary of the Invention

[0033] The present invention relates to novel proteins. More specifically, isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to these novel polypeptides. The invention further relates to screening methods for

identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

Detailed Description

Tables

100341 Table 1 summarizes some of the polynucleotides encompassed by the invention (including cDNA clones related to the sequences (Clone ID NO:Z), contig sequences (contig identifier (Contig ID:) and contig nucleotide sequence identifier (SEQ ID NO:X)) and further summarizes certain characteristics of these polynucleotides and the polypeptides encoded thereby. The first column provides the gene number in the application for each clone identifier. The second column provides a unique clone identifier, "Clone ID NO:Z", for a cDNA clone related to each contig sequence disclosed in Table 1. The third column provides a unique contig identifier, "Contig ID:" for each of the contig sequences disclosed in Table 1. The fourth column provides the sequence identifier, "SEQ ID NO:X", for each of the contig sequences disclosed in Table 1. The fifth column, "ORF (From-To)", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence of SEQ ID NO:X that delineate the preferred open reading frame (ORF) that encodes the amino acid sequence shown in the sequence listing and referenced in Table 1 as SEQ ID NO:Y (column 6). Column 7 lists residues comprising predicted epitopes contained in the polypeptides encoded by each of the preferred ORFs (SEQ ID NO:Y). Identification of potential immunogenic regions was performed according to the method of Jameson and Wolf (CABIOS, 4; 181-186 (1988)); specifically, the Genetics Computer Group (GCG) implementation of this algorithm, embodied in the program PEPTIDESTRUCTURE (Wisconsin Package v10.0, Genetics Computer Group (GCG), Madison, Wisc.). This method returns a measure of the probability that a given residue is found on the surface of the protein. Regions where the antigenic index score is greater than 0.9 over at least 6 amino acids are indicated in Table 1 as "Predicted Epitopes". In particular embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the predicted epitopes described in Table 1. It will be appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may

vary slightly. Column 8, "Tissue Distribution" shows the expression profile of tissue, cells, and/or cell line libraries which express the polynucleotides of the invention. The first number in column 8 (preceding the colon), represents the tissue/cell source identifier code corresponding to the key provided in Table 4. Expression of these polynucleotides was not observed in the other tissues and/or cell libraries tested. For those identifier codes in which the first two letters are not "AR", the second number in column 8 (following the colon), represents the number of times a sequence corresponding to the reference polynucleotide sequence (e.g., SEQ ID NO:X) was identified in the tissue/cell source. Those tissue/cell source identifier codes in which the first two letters are "AR" designate information generated using DNA array technology. Utilizing this technology, cDNAs were amplified by PCR and then transferred, in duplicate, onto the array. Gene expression was assayed through hybridization of first strand cDNA probes to the DNA array, cDNA probes were generated from total RNA extracted from a variety of different tissues and cell lines. Probe synthesis was performed in the presence of ³³P dCTP, using oligo(dT) to prime reverse transcription. After hybridization, high stringency washing conditions were employed to remove non-specific hybrids from the array. The remaining signal, emanating from each gene target, was measured using a Phosphorimager. Gene expression was reported as Phosphor Stimulating Luminescence (PSL) which reflects the level of phosphor signal generated from the probe hybridized to each of the gene targets represented on the array. A local background signal subtraction was performed before the total signal generated from each array was used to normalize gene expression between the different hybridizations. The value presented after "[array code]:" represents the mean of the duplicate values, following background subtraction and probe normalization. One of skill in the art could routinely use this information to identify normal and/or diseased tissue(s) which show a predominant expression pattern of the corresponding polynucleotide of the invention or to identify polynucleotides which show predominant and/or specific tissue and/or cell expression. Column 9 provides the chromosomal location of polynucleotides corresponding to SEQ ID NO:X. Chromosomal location was determined by finding exact matches to EST and cDNA sequences contained in the NCBI (National Center for Biotechnology Information) UniGene database. Given a presumptive chromosomal location, disease locus association was determined by comparison with the Morbid Map, derived from Online Mendelian Inheritance in Man (Online Mendelian

Inheritance in Man, OMIMTM. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD) 2000. World Wide Web URL: http://www.ncbi.nlm.nih.gov/omim/). If the putative chromosomal location of the Query overlaps with the chromosomal location of a Morbid Map entry, an OMIM identification number is disclosed in column 10 labeled "OMIM Disease Reference(s)". A key to the OMIM reference identification numbers is provided in Table 5. Column 11 provides the amino acid position of the ALOM hit(s) predicted for the amino acid sequence shown in SEQ ID NO:Y.

[0035] Table 2 summarizes homology and features of some of the polypeptides of the invention. The first column provides a unique clone identifier, "Clone ID NO:Z", corresponding to a cDNA clone disclosed in Table 1. The second column provides the unique contig identifier, "Contig ID:" corresponding to contigs in Table 1 and allowing for correlation with the information in Table 1. The third column provides the sequence identifier, "SEQ ID NO:X", for the contig polynucleotide sequence. The fourth column provides the analysis method by which the homology/identity disclosed in the Table was determined. Comparisons were made between polypeptides encoded by the polynucleotides of the invention and either a non-redundant protein database (herein referred to as "NR"), or a database of protein families (herein referred to as "PFAM") as further described below. The fifth column provides a description of the PFAM/NR hit having a significant match to a polypeptide of the invention. Column six provides the accession number of the PFAM/NR hit disclosed in the fifth column. Column seven, "Score/Percent Identity", provides a quality score or the percent identity, of the hit disclosed in columns five and six. Columns 8 and 9, "NT From" and "NT To" respectively, delineate the polynucleotides in "SEQ ID NO:X" that encode a polyneptide having a significant match to the PFAM/NR database as disclosed in the fifth and sixth In specific embodiments polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence encoded by a polynucleotide in SEQ ID NO:X as delineated in columns 8 and 9, or fragments or variants thereof.

[0036] Table 3 provides polynucleotide sequences that may be disclaimed according to certain embodiments of the invention. The first column provides a unique clone identifier, "Clone ID", for a cDNA clone related to contig sequences disclosed in Table 1. The

second column provides the sequence identifier, "SEQ ID NO:X", for contig sequences disclosed in Table 1. The third column provides the unique contig identifier, "Contig ID:", for contigs disclosed in Table 1. The fourth column provides a unique integer 'a' where 'a' is any integer between 1 and the final nucleotide minus 15 of SEQ ID NO:X, and the fifth column provides a unique integer 'b' where 'b' is any integer between 15 and the final nucleotide of SEQ ID NO:X, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:X, and where b is greater than or equal to a + 14. For each of the polynucleotides shown as SEQ ID NO:X, the uniquely defined integers can be substituted into the general formula of a-b, and used to describe polynucleotides which may be preferably excluded from the invention. In certain embodiments, preferably excluded from the invention are at least one, two, three, four, five, ten, or more of the polynucleotide sequence(s) having the accession number(s) disclosed in the sixth column of this Table. In further embodiments, preferably excluded from the invention are the specific polynucleotide sequence(s) contained in the clones corresponding to at least one, two, three, four, five, ten, or more of the available material having the accession numbers identified in the sixth column of this Table.

[0037] Table 4 provides a key to the tissue/cell source identifier code disclosed in Table 1, column 8. Column 1 provides the tissue/cell source identifier code disclosed in Table 1, Column 8. Columns 2-5 provide a description of the tissue or cell source. Codes corresponding to diseased tissues are indicated in column 6 with the word "disease". The use of the word "disease" in column 6 is non-limiting. The tissue or cell source may be specific (e.g. a neoplasm), or may be disease-associated (e.g., a tissue sample from a normal portion of a diseased organ). Furthermore, tissues and/or cells lacking the "disease" designation may still be derived from sources directly or indirectly involved in a disease state or disorder, and therefore may have a further utility in that disease state or disorder. In numerous cases where the tissue/cell source is a library, column 7 identifies the vector used to generate the library.

[0038] Table 5 provides a key to the OMIM reference identification numbers disclosed in Table 1, column 10. OMIM reference identification numbers (Column 1) were derived from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of

Medicine, (Bethesda, MD) 2000. World Wide Web URL: http://www.ncbi.nlm.nih.gov/omim/). Column 2 provides diseases associated with the cytologic band disclosed in Table 1, column 9, as determined using the Morbid Map database.

[0039]

Definitions

[0040] The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

[0041] In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide. The term "isolated" does not refer to genomic or cDNA libraries, whole cell total or mRNA preparations, genomic DNA preparations (including those separated by electrophoresis and transferred onto blots), sheared whole cell genomic DNA preparations or other compositions where the art demonstrates no distinguishing features of the polynucleotide/sequences of the present invention.

[0042] As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence encoding SEQ ID NO:Y or a fragment or variant thereof; a nucleic acid sequence contained in SEQ ID NO:X (as described in column 3 of Table 1) or the complement thereof; a cDNA sequence contained in Clone ID NO:Z (as described in column 2 of Table 1 and contained within the ATCC Deposit). For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having an amino acid sequence encoded by a

polynucleotide of the invention as broadly defined (obviously excluding poly-Phenylalanine or poly-Lysine peptide sequences which result from translation of a polyA tail of a sequence corresponding to a cDNA).

[0043] In the present invention, "SEQ ID NO:X" was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X is deposited at Human Genome Sciences, Inc. (HGS) in a catalogued and archived library. As shown, for example, in column 2 of Table 1, each clone is identified by a cDNA Clone ID (identifier generally referred to herein as Clone ID NO:Z). Each Clone ID is unique to an individual clone and the Clone ID is all the information needed to retrieve a given clone from the HGS library. Furthermore, clones disclosed in this application have been deposited with the ATCC on March 24, 2000, having the ATCC designation numbers PTA-1559. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

[0044] In specific embodiments, the polynucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polynucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polynucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

[0045] A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, or the complement thereof (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments described herein), the polynucleotide sequence delineated in columns 8 and 9 of Table 2 or the complement thereof, and/or cDNA sequences contained in Clone ID NO:Z (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments, or the cDNA clone within the pool of

cDNA clones deposited with the ATCC, described herein). "Stringent hybridization conditions" refers to an overnight incubation at 42 degree C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65 degree C.

[0046] Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37 degree C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH₂PO₄; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50 degree C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

[0047] Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

[0048] Of course, a polynucleotide which hybridizes only to polyA+ sequences (such as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone generated using oligo dT as a primer).

[0049] The polynucleotide of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and

double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

The polypeptide of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing. phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA

mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth. Enzymol. 182:626-646 (1990); Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992)).

[0051] "SEQ ID NO:X" refers to a polynucleotide sequence described, for example, in Tables 1 or 2, while "SEQ ID NO:Y" refers to a polypeptide sequence described in column 6 of Table 1. SEQ ID NO:X is identified by an integer specified in column 4 of Table 1. The polypeptide sequence SEQ ID NO:Y is a translated open reading frame (ORF) encoded by polynucleotide SEQ ID NO:X. "Clone ID NO:Z" refers to a cDNA clone described in column 2 of Table 1.

[0052] "A polypeptide having functional activity" refers to a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide for binding) to an anti-polypeptide antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

[0053] The polypeptides of the invention can be assayed for functional activity (e.g. biological activity) using or routinely modifying assays known in the art, as well as assays described herein. Specifically, one of skill in the art may routinely assay polypeptides (including fragments and variants) of the invention for activity using assays as described in the Examples.

[0054] "A polypeptide having biological activity" refers to a polypeptide exhibiting activity similar to, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not

PCT/US01/16450 WO 01/90304

more than about three-fold less activity relative to the polypeptide of the present invention).

[0055] Table 1 summarizes some of the polynucleotides encompassed by the invention (including contig sequences (SEQ ID NO:X) and clones (Clone ID NO:Z) and further summarizes certain characteristics of these polynucleotides and the polypeptides encoded thereby.

Polynucleotides and Polypeptides of the Invention

It has been discovered herein that the polynucleotides described in Table 1 are predicted to be localized to the plasma membrane of human cells. Accordingly, such polynucleotides, polypeptides encoded by such polynucleotides, and antibodies specific for such polypeptides find use in the diagnosis, treatment, and prevention of diseases associated with cell proliferation and cell signaling, particularly cancer, immune response and neuronal disorders.

Plasma membrane localization was predicted using the following method. All novel contigs in the HGS database were scored using the ALOM program developed by Klein et al. to detect potential transmembrane segments (Klein, P. et al. Biochim. Biophys. Acta 815:468 (1985); which is hereby incorporated by reference in its entirety herein). ALOM attempts to identify the most probable transmembrane segment from the average hydrophobicity value of 17-residue segments, if any. It predicts whether the segment is a transmembrane segment (INTEGRAL) or not (PERIPHERAL) comparing the discriminant score (reported as 'value') with a threshold parameter pre- defined to 0.0 for bacteria ('threshold'). For an integral membrane protein, position(s) of transmembrane segment(s) are also reported. Their length is fixed to 17 but their extension, i.e., the maximal range that satisfies the discriminant criterion, is also given in parentheses. The discrimination step mentioned above is continued after leaving out the segment till there remains no predicted transmembrane segment. The item 'count' is the number of predicted transmembrane segments.

The protein sequence used was the longest start-codon to stop-codon (or end of sequence) ORF. If the ORF was at least 100 amino acids long, and there was a predicted INTEGRAL membrane domain starting at least 40 amino acids downstream of the start

Met, the contig was selected as encoding a plasma-membrane-associated protein. The polynucleotides of the invention are predicted to be plasma membrane associated and comprise the predicted INTEGRAL membrane domains for each unique contig ID shown in column 11 of Table 1.

FABLE 1

				_																						
ALOM	Results			44-60							104-120,	83-99						80-104,	20-37, 56-	72, 134	150			40-57		
OMIM	Disease	Reference(s):																								
Cytologic	Band																									
Tissue Distribution	Library code: count	(see Table IV for Library	Codes)	AR039: 9, AR033: 5,	AR053: 5, AR089: 4,	AR096: 4, AR104: 4,	AR055: 4, AR060: 4,	AR052: 3, AR061: 3	L0619: 1, H0059: 1 and	H0423: 1.	AR055: 15, AR060: 9,	AR052: 7, AR061: 7,	AR089: 6, AR033: 6,	AR053: 5, AR096: 3,	AR104: 1, AR039: 0	L0748: 2, H0328: 1 and	H0529: 1.	AR060: 6, AR055: 3,	AR053: 3, AR096: 2,	AR089: 2, AR061: 2,	AR033: 2, AR052: 1,	AR039: 1, AR104: 1	H0031: 1	AR055: 9, AR060: 6,	AR096: 5, AR089: 5,	AR033: 4, AR052: 4,
Predicted Epitopes	1			1416 Arg-23 to Leu-33,	Thr-61 to Phe-73.																•		•			
AA	SEQ	a	NO: Y	1416							1417							1418					_	1419		
ORF	(From-	To)		64 - 471							144-	572						81 - 530						171 -	530	
SEQ	A	NO: X		11							12							13						14		
Contig	ä	NO: X		413036							456287						٠	463734				•		465120		
Gene Clone ID	NO: Z			HCFNH88	-						HODDW3 456287	7		,***	,,		•	HPMFI38			-			HLTDP38		
Gene	No:										2							3						4		•

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	90-113, 59-78, 2- 18, 28-44	31-57, 63- 85, 4-23	126-143
			126650, 126650, 164860, 180105, 222800,
			7q31
AR061: 4, AR053: 3, AR039: 2, AR104: 1 L0662: 3, L0803: 2, L0805: 2, T0002: 1, H0090: 1, H0412: 1, L0794: 1, L0804: 1, L0655: 1, L0647: 1, L0666: 1 and L0663: 1.	AR055: 6, AR060: 4, AR052: 4, AR061: 3, AR039: 3, AR089: 3, AR053: 3, AR096: 3, AR033: 3, AR104: 2 L0615: 1, S0420: 1, H0333: 1, H0286: 1, H0634: 1, H0144: 1 and H0423: 1.	AR033: 8, AR055: 5, AR053: 3, AR089: 3, AR052: 3, AR061: 3, AR039: 3, AR060: 3, AR104: 2, AR096: 2 L0756: 4, L0439: 2, S0412: 2, S0222: 1, H0327: 1, H0009: 1, L0157: 1 and S0031: 1.	AR089: 7, AR096: 6, AR053: 5, AR060: 5, AR052: 4, AR039: 4, AR104: 4, AR055: 4, AR033: 3, AR061: 1
	1420 Gln-20 to Ala-26, Ser-53 to Glu-60.		Met-1 to Phe-6, AR089: Ser-12 to Asp-17, AR053: Ser-100 to Ser-105, AR052: Arg-163 to Asp-176, AR104: Val-192 to Glu-199, AR033:
	1420	1421	1422
	15 - 365	164 - 595	67 - 723
	15	16	17
	465711	466000	488966
	HMHBT30 465711	HFCBA57	HSRAL33
	'n	9	7

	89-105	72-90
246900, 274600, 274600, 602081		-
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L0777: 4, L0766: 3, H0014: 2, L0731: 2, L0758: 2, S0282: 1, S0007: 1, S0280: 1, H0575: 1, H0328: 1, L0369: 1, L0637: 1, L0771: 1, L0768: 1, L0803: 1, L0655: 1, L0809: 1, S0380: 1, H0521: 1, H0627: 1, S3014: 1, L0748: 1, L0608: 1, S0011: 1 and S0192: 1.	AR055: 8, AR052: 5, AR033: 4, AR061: 4, AR060: 4, AR089: 3, AR096: 3, AR039: 3, AR104: 3, AR053: 3 L0596: 2, L0588: 2, H0135: 1, H0056: 1, L0369: 1, L0803: 1, H0520: 1, S0027: 1 and S0276: 1.	AR060: 140, AR055: 117, AR104: 113, AR039: 111, AR061: 92, AR033: 72, AR083: 70, AR052: 66, AR089: 55, AR096: 21 L0748: 5, L0749: 5, L0439: 3, L0779: 2, L0731: 2, H0556: 1, S0356: 1, H0575: 1, H0597: 1, H0551:
	1423 Pro-52 to Pro-57.	1424 Leu-9 to Arg-18, Phe-109 to Gly-115.
	1423	1424
	20 - 415	74 - 424
•	18	19
	502907	503441
	HSSMQ84	HUKAB82 503441
	∞	6

52-68	100-118
9: 1, 10655: 1: 1, 6: 1. 6: 1. 6: 1, 1: 3, 1: 3, 1: 3, 1: 1, 1: 1, 1: 1, 1: 1, 1: 1, 1: 1, 1: 1, 1: 1,	, 50028: 352: 1. 5, 1. 4, 2, 2, 1.0768: 1.2, 1.0768:
1, H0413: 1, H0059: 1, L0770: 1, L0771: 1, L0655: 1, H0144: 1, S0378: 1, L0747: 1 and S0276: 1. AR096: 4, AR033: 3, AR039: 3, AR089: 3, AR055: 3, AR089: 3, AR056: 2, AR053: 1, AR060: 1, AR104: 1 L0766: 4, H0617: 2, L0662: 2, H0690: 2, H0295: 1, H0662: 1, R0354: 1, H0729: 1, H0318: 1, H0545: 1, H0266: 1, H0401: 1, H0729: 1, L0523: 1, H0739: 1, L0523: 1, L0803: 1, L0523: 1, L0338: 1, L0665: 1, H0703: 1, H0539: 1, H0521: 1,	HU522: 1, SU400: 1, SU028: 1, LO779: 1 and H0352: 1. AR052: 5, AR053: 5, AR096: 4, AR096: 4, AR039: 2, AR060: 3, AR039: 2, AR060: 3, AR061: 2 L0775: 3, H0624: 2, L07768: 2, H0659: 2, L0759: 2, L0768: 2, H0659: 2, L0759: 2, L0605: 2, S0192: 2, S0114:
1, H0413 L0770: 1 L0747: 1 AR039: AR055: AR060: L0766: 2, L0766: 4 L0766: 4 L	.0
	1426 Met-1 to Arg-11, Gly-30 to Arg-39.
1425	1426
29 - 328	72 - 425
20	21
506828	506893
HDPP46	(B11
	HMTME11

WO 01/90304	PCT/US01/1645
	941, 83- 106, 54-76
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1, S0116: 1, H0638: 1, H0125: 1, H0489: 1, S0222: 1, L0623: 1, T0115: 1, H0327: 1, H0687: 1, T0023: 1, H0031: 1, H0673: 1, L0065: 1, L0520: 1, L0769: 1, L0653: 1, L0783: 1, L0809: 1, L0519: 1, L0543: 1, H0672: 1, S0310: 1, L0777: 1, S0380: 1, H0670: 1, H0436: 1, S0312: 1, L0777: 1, L0731: 1, H0653: 1, H0543: 1, H0422: 1 and H0543: 1, H0422: 1 and	AR055: 11, AR060: 8, AR033: 5, AR061: 5, AR052: 5, AR089: 4, AR104: 4, AR096: 4, AR039: 4, AR053: 4 L0439: 4, L0803: 3, H0590: 2, L0483: 2, H0163: 2, L0805: 2, S0374: 2, H0658: 2, H0696: 2, H0717: 1, S0116: 1, S0358: 1, L0717: 1, H0052: 1, H0194: 1, H0184: 1, L0738: 1, H0545: 1, S0316: 1, S0003: 1, S0364: 1, S0366: 1, S0036: 1, H0272: 1, L0638:
	1427
	12 - 386
	23
	507310
	HBMUK46
·	12

	138-154, 8-24	62-89, 25- 46
	·	·
1, L0766: 1, L0776: 1, L0789: 1, L0664: 1, L0665: 1, H0710: 1, H0521: 1, S0013: 1, S0406: 1, L0744: 1, L0752: 1, L0758: 1, L0605: 1, S0026: 1 and H0543: 1.	AR052: 319, AR096: 250, AR089: 171, AR104: 71, AR053: 121, AR104: 71, AR039: 57, AR033: 51, AR061: 51, AR055: 14 L0752: 3, L0748: 2, L0740: 2, L0731: 2, S0358: 1, H0438: 1, H0574: 1, H0046: 1, H0041: 1, H0272: 1, S0150: 1, L0794: 1, L0803: 1, L0804: 1, L0775: 1, L0661: 1, L0789: 1, H0672: 1, H0539: 1, L0758: 1 and S0436: 1.	AR033: 1, AR089: 1, AR053: 1, AR104: 1, AR061: 1, AR096: 0, AR055: 0, AR060: 0, AR052: 0 L0766: 6, L0740: 5, H0135: 1, L0769: 1, L0383: 1, S0044: 1, L0750: 1 and
		Pro-15 to Ser-21, Ser-60 to Tyr-65, Glu-90 to Asp-101.
	1428	1429
	25 - 597	
	ಜ	42
	509728	521848
	HETDT70	HPWBL19
	E1	14

88-104, 49-65	
1 1	
AR033: 2, AR053: 2, AR089: 1, AR104: 1, AR060: 1, AR096: 0, AR089: 0, AR039: 0, AR039: 0, AR039: 0, AR039: 1, L0759: 1, L0759: 1, AR096: 1, AR096: 1, AR096: 1, AR096: 1, AR096: 1, AR096: 1, AR033: 1, AR096: 1, AR052: 0, AR039: 0, AR039: 0, AR039: 0, AR039: 0, AR039: 4, L0439: 4, L0438: 4, L0439: 4, L0762: 2, L0762: 2, L0776: 1, H0580: 1, H0716: 1, H0459: 1, R0776: 2, L0776: 2, L0776: 1, H0580: 1, H0716: 1, L0005: 1, H0580: 1, H0716: 1, L0005: 1, H0580: 1, H0716: 1, L0005: 1, H0580: 1, H0716: 1, H0716: 1, H0751:	1, 50040: 1, HUB12: 1, H0586: 1, H0050: 1, L0471: 1, H0615: 1, H0488: 1, S0426: 1, H0529: 1, L0520: 1, L0638: 1, L0667: 1,
Lys-12 to Lys-17, Thr-39 to Lys-45, Thr-59 to Glu-57, Glu-80 to Ile-90, Gly-122 to Met-127, Lys-170 to Asn-177.	•
1431	
68 - 598	
8 8	
523186	
HE9NE12	
15	

	81-102, 22-38	31
	148370	
	8p23	
L0373: 1, L0378: 1, L0805: 1, L0659: 1, L0526: 1, L0809: 1, L0663: 1, S0374: 1, H0711: 1, H0670: 1, H0521: 1, L0777: 1, L0780: 1, L0485: 1, L0697: 1, S0192: 1, H0543: 1, H0423: 1 and H0506: 1.	AR053: 4, AR061: 4, AR052: 3, AR055: 3, AR039: 3, AR060: 3, AR089: 2, AR096: 2, AR033: 1, AR104: 1 H0170: 2	AR055: 16, AR061: 7, AR052: 7, AR060: 6, AR033: 5, AR089: 5, AR053: 5, AR086: 3, AR039: 0, AR104: 0 H0052: 5, L0748: 5, L0756: 4, L0731: 4, S0360: 3, L0764: 3, L0747: 3, L0749: 3, H0255: 2, H0333: 2, L0055: 2, L0653: 2, L0740: 2, L0754: 2, L0750: 2, L0596: 2, H0352: 2, H0556: 1, H0341: 1, H0662: 1, H0306: 1, H0402: 1, H0036: 1, H0434: 1, H0150:
	1432 Leu-15 to Ser-21.	Arg-56 to Phe-61.
	12 - 317 1432	53 - 376 1433
	27 1	28
	525950	527491
	HE2AX73	HHGBV89
	17	81

		
	48-65	125-157, 4-29, 67- 86, 36-52, 106-122
		,
1, H0059: 1, L0521: 1, H0684: 1, L0755:	14, 11, 10, 9, 8 H0333: 1, L0666: 1, L0758:	1, 1, 1, 0, 0, 3, \$0282:
1, H0252: 1, L0456: 1, H0135: 1, H0413: 1, H0059: 1, H0529: 1, L0770: 1, L0769: 1, L0630: 1, L0521: 1, L0662: 1, L0775: 1, L0776: 1, L0493: 1, H0684: 1, S0328: 1, S0044: 1, L0777: 1, L0752: 1, L0755: 1, L0758: 1 and S0242: 1.	AR039: 14, AR055: 14, AR033: 11, AR053: 11, AR052: 11, AR060: 10, AR104: 10, AR096: 9, AR089: 8, AR061: 8 S0380: 2, L0742: 2, L0779: 2, L0759: 2, H0333: 1, H0039: 1, H0040: 1, H0625: 1, H0561: 1, L0666: 1, L0663: 1, H0672: 1, L0747: 1, L0777: 1, L0758: 1 and H0444: 1.	AR089: 1, AR061: 1, AR053: 1, AR096: 1, AR050: 1, AR104: 1, AR033: 0, AR055: 0, AR039: 0, AR052: 0 L0777: 5, S0436: 5, S0116: 3, L0805: 3, L0809: 3, H0696: 3, H0423: 3, S0282:
1, H0252 H0135: 1 1, H0529 L0769: 1 1, L0662 L0776: 1 1, S0328 1, L0777: 1	AR039: 14, AR AR033: 11, AR AR052: 11, AR AR104: 10, AR AR089: 8, AR S0380: 2, L07- L0779: 2, L075 1, H0039: 1, H05 H0625: 1, H05 1, L0663: 1, H05 L0747: 1, L077	dada win
	Lys-13 to Asp-24, Pro-32 to Arg-40.	Asn-54 to Gly-60, Pro-166 to Pro-171.
	1434 P.D.	1435 Pr
	1 - 405	531 - 16
	53	30
	529791	532045
	HTTDC06	HFXKR35
	61	20

77

	49-65	49-65	46-62, 26- 42
			114240, 224120, 600839, 602099
			15q15.1
AR104: 2, AR089: 2, AR096: 2, AR052: 2 S0007: 3, S0001: 1, H0618: 1, H0009: 1, S0051: 1, L0763: 1, L0439: 1 and L0758: 1.	AR033: 54, AR055: 51, AR061: 43, AR089: 40, AR053: 38, AR060: 38, AR052: 26, AR096: 11, AR104: 10, AR039: 5 H0038: 2	AR033: 112, AR052: 80, AR096: 68, AR053: 67, AR089: 65, AR104: 61, AR060: 58, AR061: 55, AR039: 52, AR055: 38 H0052: 2, H0616: 2, L0779: 2, L0777: 2, H0656: 1, H0549: 1, H0038: 1, L0748: 1, L0758: 1, L0601: 1 and H0543: 1.	AR055: 17, AR053: 9, AR060: 9, AR033: 9, AR061: 8, AR039: 7, AR089: 6, AR052: 6, AR104: 6, AR096: 5 S0418: 3, L0439: 3, L0595: 2, H0542: 2, H0656:
	Pro-15 to Thr-24, Glu-39 to Trp-47.	Arg-14 to Asp-20.	
	1437	1438	1439
	88 - 438	37 - 453	156 - 488
	32	83	34
	535036	535040	536712
	HTECA32	нтенг79	HPJBL54
		ន	24

<u> </u>	13- -78	
	81-98, 13- 29, 175- 191, 62-78	177-193, 149-165
1, H0638: 1, S0420: 1, S0045: 1, H0253: 1, H0267: 1, H0553: 1, S0150: 1, L0438: 1, H0519: 1, S0126: 1, H0660: 1, S0152: 1 and H0543: 1.	AR096: 1, AR055: 1, AR089: 1, AR060: 1, AR039: 1, AR033: 0, AR061: 0, AR053: 0, AR052: 0, AR104: 0 S0028: 3, S0001: 2, H0617: 2, L0361: 2, S0356: 1, S0045: 1, H0619: 1, S0278: 1, H0250: 1, H0231: 1, H0181: 1, S0390: 1 and S0031: 1.	AR052: 3, AR096: 2, AR053: 2, AR033: 2, AR089: 2, AR061: 2, AR060: 1, AR055: 1, AR104: 1, AR039: 0 L0789: 4, H0306: 2, L0809: 2, L0759: 2, L0596: 2, H0402: 1, H0580: 1, H0550: 1, H0486: 1, H0559: 1, H0486: 1, H0031: 1, H0674: 1, H0135: 1, H0100: 1, L0800: 1,
1, H0638: 1, S0420: 1, S0045: 1, H0253: 1, H0253: 1, H0253: 1, S0150: 1, L0438: 1, H0519: 1, S01241, H0660: 1, S0152: 1 and H0543: 1.	AR096: 1, AR055: 1, AR039: 1, AR060: 1, AR039: 1, AR033: 0, AR061: 0, AR053: 0, AR052: 0, AR104: 0 S0028: 3, S0001: 2, H0617: 2, L0361: 2, S035 1, S0045: 1, H0619: 1, S0278: 1, H0250: 1, H023 1, H0181: 1, S0390: 1 and S0031: 1.	AR052: 3, AR096: 2, AR053: 2, AR033: 2, AR089: 2, AR061: 2, AR060: 1, AR055: 1, AR104: 1, AR039: 0 L0789: 4, H0306: 2, L0809: 2, L0759: 2, L0596: 2, H0402: 1, H0580: 1, H0550: 1, H0548: 1, H0559: 1, H0448: 1, H0031: 1, H0674: 1, H0135
1, H0638 S0045: 1 1, H0553 L0438: 1 1, H0660 H0543: 1	AR096: AR039: AR052: AR052: S0028: H0617: 2 1, S0045 S0278: 1 1, H0181	AR052: AR053: AR069: AR104: L0789: 2, L0809: 2, 2, H0402: H0550: 1, 1, H0559: H010031: 1,
	3lu-59.	
	1440 Asp-46 to Glu-59.	
-	1440	1441
	64 - 753	588-929
	35	
	538217	550208
	HSDDD20	HCUCG74
	23	26

WO 01/90304	·	PC1/USU1/10
	38-59	7-37, 89-
L0794: 1, L0804: 1, L0805: 1, L0515: 1, L0783: 1, H0672: 1, L0777: 1, H0444: 1 and H0352: 1.	AR033: 4, AR089: 3, AR060: 2, AR055: 2, AR052: 1, AR053: 1, AR061: 1, AR096: 0, AR039: 0, AR104: 0 S0242: 1 and S0196: 1.	AR069: 45, AR096: 43, AR055: 27, AR104: 20, AR053: 20, AR052: 19, AR053: 14, AR061: 14 H0250: 60, S0126: 24, H0013: 9, H0124: 9, H0494: 8, H0521: 7, H0428: 6, H0553: 6, H0644: 6, H0038: 6, S0027: 6, S0040: 5, T0039: 5, H050: 5, L0471: 5, H0135: 5, H0551: 5, L0740: 5, H0171: 4, S0356: 4, S0046: 4, H0586: 4, H0486: 4, H0599: 4, H0046: 4, H0024: 4, H0266: 4,
	·	Pro-69 to Gln-77.
	1442	1443
	96 - 404	24 - 362
	37	86
	550992	551777
	HFIXK94	HPJAV46
	72	78
		

O 01/90304		····		PCT/US01/1645
03: 4, 2: 3, H0574: 3: 3, H0014: 373: 3, H0547:	522: 3, 4: 2, H0265: 112: 2, 1: 2, H0125: 208: 2.	7: 2, H0645: 431: 2, 7: 2, H0575: 49: 2,	5: 2, H0012: 179: 2, 5: 2, H0039: 032: 2, 0: 2, H0616:	25. 2, 20294: 17: 2, H0506: 294: 1, 2: 1, S0420: 76: 1, 1: 1, H0393: 369: 1,
4, S0152: 4, L0603: 4, H0556: 3, S0222: 3, H0574: 3, H0156: 3, S0010: 3, H0581: 3, H0620: 3, H0014: 3, H0015: 3, H0373: 3, S0022: 3, H0031: 3, H0547:	3, H0519; 3, H0522; 3, L0748; 3, H0624; 2, H0265; 2, H0295; 2, S0212; 2, H0484; 2, H0661; 2, H0125; 2, S0418; 2, H0208; 2,	S0045: 2, H0619: 2, H0645: 2, H0550: 2, H0431: 2, H0370: 2, H0427: 2, H0575: 2, H0618: 2, S0049: 2,	H0530: 2, H0545: 2, H0012: 2, H0375: 2, H0179: 2, H0286: 2, H0615: 2, H0039: 2, H0622: 2, H0032: 2, H0068: 2, H0090: 2, H0616:	2, 1102.57. 2, 1102.03. 2, H0100: 2, T0042: 2, S0294: 2, S0142: 2, H0517: 2, H0651: 2, S0037: 2, H0506: 2, H0157: 1, H0294: 1, H0671: 1, H0662: 1, S0420: 1, S0358: 1, S0376: 1, S0360: 1, H0580: 1, H0393: 1, H0437: 1, H0369: 1, H0549: 1, H0357: 1, H0409-
			 	
	-	-		

	42-67, 3- 19	36-61, 92- 110	1-33, 230- 247, 125- 141
1, L0593: 1, L0595: 1, S0011: 1, H0668: 1, S0026: 1, S0446: 1 and H0293: 1.	AR052: 16, AR096: 14, AR052: 14, AR055: 13, AR089: 11, AR060: 9, AR033: 9, AR104: 6, AR061: 5, AR039: 3 H0038: 8, H0616: 4, L0779: 3, L0758: 3, L0753: 2, L0032: 1, T0006: 1, H00040: 1, S0002: 1, L0768: 1, S0053: 1 and H0547: 1.	AR039: 13, AR053: 11, AR055: 9, AR089: 9, AR033: 9, AR060: 7, AR096: 7, AR052: 7, AR061: 5, AR104: 5 S0222: 1	AR052: 4, AR061: 3, AR055: 3, AR053: 3, AR089: 2, AR033: 2, AR060: 2, AR039: 1, AR096: 1, AR104: 1 S0002: 70, S0426: 29, S0Z78: 28, S0003: 28, H0521: 28, S0344: 27, S0142: 14, L0747: 14, H0090: 13, S0144: 13,
		Ser-60 to Ser-66.	Arg-35 to Cys-46, Phe-52 to Met-57, Thr-70 to Gly-84, Thr-88 to Glu-109, Gly-151 to Gly-159, Ser-167 to Thr-175, Ala-193 to Phe-206, Arg-215 to Gly-223.
	1444	1445	1446
	21 - 329	1235 - 885	401 - 1144
	36	9	14
	558312	561612	562024
	HITDL61	HFPBN94	HYBBG69
	29	30	31

	35-62
1, H0638: 1, S0358: 1, S0376: 1, T0008: 1, S0132: 1, H0645: 1, H0645: 1, H0635: 1, H0645: 1, H0635: 1, H06427: 1, S0280: 1, L0022: 1, T0082: 1, H0036: 1, H0620: 1, H0036: 1, H0639: 1, H0620: 1, H0644: 1, H0639: 1, H0674: 1, H0673: 1, S6028: 1, H0673: 1, H0674: 1, L0142: 1, L0143: 1, H0673: 1, H0674: 1, L0143: 1, H0674: 1, S0364: 1, H0674: 1, L0763: 1, L0763: 1, L0763: 1, L0763: 1, L0764: 1, L0561: 1, L0769: 1, L0764: 1, L0576: 1, L0776: 1, L0657: 1, L0776: 1, L0782: 1, L0776: 1, L0657: 1, L0782: 1, L0776: 1, L0657: 1, L0783: 1, L0776: 1, L0553: 1, L0776: 1, L0657: 1, L0788: 1, L0776: 1, L0657: 1, H0635: 1, L0788: 1, L0787: 1, H0655: 1, L0788: 1, L0787: 1, H0655: 1, L0788: 1, L0787: 1, H0555: 1, L0788: 1, L0788: 1, L0787: 1, H0555: 1, L0788: 1, L0787: 1, H0555: 1, L0788: 1, L0788: 1, L0788: 1, L0787: 1, H0555: 1, L0788: 1, L0	AR096: 1, AR089: 1,
	1447 Met-1 to Gly-6, A
	350-
	562077 42
	32 HDPOJ05

VO 01/90304	PCT/US01/1645
	42-66, 67- 84, 9-25
AR061: 0, AR055: 0, AR033: 0, AR104: 0, AR053: 0, AR104: 0, AR060: 0 H0250: 5, L0740: 4, H0657: 3, L0761: 3, L0659: 3, L0809: 3, L0717: 2, H0620: 2, H0135: 2, H0063: 2, H0100: 2, L0789: 2, L0751: 2, L0750: 2, L0731: 2, H0543: 2, S0116: 1, H0255: 1, H0664: 1, H0580: 1, H0617: 1, H0664: 1, H0421: 1, H0123: 1, H0179: 1, L0794: 1, L0766: 1, H050: 1, L0655: 1, L0783: 1, L0532: 1, L0666: 1, H0520: 1, H0547: 1, H0660: 1, H0548: 1, S0380: 1, H0521: 1, H0522: 1, H0555: 1, L0756: 1, L0779: 1, S0436: 1 and S0276: 1.	AR052: 7, AR053: 4, AR089: 3, AR060: 3, AR096: 3, AR033: 2, AR061: 2, AR039: 2, AR055: 2, AR104: 2 S0278: 1 and H0445: 1.
Pro-23 to Asp-37.	Leu-30 to Thr-35, Phe-38 to Gly-44.
	1448
5	39 - 428
•	43
	562775
	HMAGF64
	33

WO 01/90304		PCT/US01	/164
138-155, 83-99, 35- 51, 59-75	23-40, 50- 66	71-87, 98-	73-89,
AR053: 12, AR052: 11, AR089: 8, AR096: 8, AR055: 7, AR060: 7, AR033: 5, AR061: 5, AR104: 4, AR039: 3 T0023: 2, L0662: 2, S0330: 2, L0749: 2, L0758: 2, S0356: 1, S0358: 1, S0360: 1, S0408: 1, L0586: 1, S0280: 1, H0590: 1, H0581: 1, H0052: 1, H0014: 1, S0203: 1, H0316: 1, H0591: 1, S0450: 1, S0150: 1, S0426: 1, L0747: 1, L0756: 1, S0426: 1, L0747: 1, L0756: 1, S0216: 1, L0747: 1, L0756: 1	AR039: 35, AR053: 29, AR104: 28, AR033: 25, AR052: 23, AR096: 22, AR055: 19, AR089: 18, AR060: 13, AR061: 10 H0555: 1	AR096: 2, AR089: 1, AR039: 1, AR052: 1, AR033: 1, AR104: 1, AR060: 0, AR061: 0, AR055: 0 H0600: 1 and S0002: 1.	AR096: 14, AR089: 12,
1449 Lys-14 to Asp-24, AR053: Glin-114 to Leu-119, AR089: Asp-122 to Arg-127. AR053: AR104: T0023: S0330: 2, S0356: 1, S0286: H0591: 1, S0426: 1,	1450 Met-1 to Gly-6. ARABATE	- ABABABABABABABABABABABABABABABABABABAB	AF
		- 1451	73 1452
44 700 700	45 14 - 355	46 296 - 670	47 93 - 473
	567314 4	571474 4	572607 4
34 HACCO38 563589	HRAAM31	HWDAA0 3	HTHCV60
8	35	36	37

84-101	68-88	81-115
10, 7, 5, 1 1 0618: 1144:	3, 5, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,	2, 5, 5, 5, 7, 7, 7, 7, 7, 7, 7, 7, 7, 7, 7, 7, 7,
4, AR033: 1 9, AR055: 7 7, AR089: 7 5, AR052: 5 5, AR061: 4 1, L0438: 2, H0427: 1, H 1, H0284: 1, H0494: 1, St	4, AR096: 3 3, AR052: 3 2, AR055: 2 1, AR061: 1 1, AR039: 0	AR055: 11, AR060: AR052: 5, AR089: 5 AR061: 5, AR033: 5 AR096: 4 AR039: 4, AR104: 3 L0747: 3, L0754: 2,
AR039: 1 AR053: 9 AR104: 7 AR096: 4 AR060: 1 L0741: 3 S0222: 1, 1, H0253: 50038: 1, 1, L0743:	AR089: AR033: AR050: AR053: AR104: H0422: 2	AR055: 1 AR052: AR061: 3 AR053: 3 AR039: 4
·	Lys-22 to Gly-28, Lys-39 to Glu-48, Ser-54 to Trp-59.	1455 His-13 to Ser-21.
1453	1454	1455
15 - 428	70 - 438	700
48	49	50
573110	573179	573751
HTLEV 17	HCFAB91	HMWEE18 573751
<u> </u>	<u> </u>	4
	AR039: 14, AR033: 10, AR051: 9, AR055: 7, AR104: 7, AR089: 7, AR096: 6, AR052: 5, AR060: 5, AR061: 4 L0741: 3, L0438: 2, S0222: 1, H0427: 1, H0618: 1, H0253: 1, H0294: 1, S0144: 1, L0743: 1 and L0366: 1.	573110 48 15 - 428 1453 AR053: 14, AR033: 10, AR053: 9, AR055: 7, AR104: 7, AR089: 7, AR104: 7, AR089: 7, AR096: 6, AR052: 5, AR061: 4 L0741: 3, L0438: 2, S0222: 1, H0427: 1, H0618: 1, H0253: 1, H0494: 1, S0144: 1, L0743: 1 and L0366: 1. 573179 49 70 - 438 1454 Lys-22 to Gly-28, AR089: 4, AR096: 3, Lys-39 to Glu-48, AR033: 3, AR052: 3, Ser-54 to Trp-59. AR060: 2, AR055: 2, AR061: 1, AR039: 1 and L0422: 2, H0339: 1 and L0769: 1.

VO 01/90304	PC1/080	1/104
	46-62	61-79
L0599: 2, H0713: 1, H0341: 1, S0360: 1, H0601: 1, H0592: 1, H0123: 1, H0494: 1, H0660: 1, L0756: 1 and L0779: 1.	AR053: 16, AR052: 14, AR096: 12, AR089: 10, AR104: 7, AR060: 6, AR055: 6, AR033: 5, AR061: 3, AR039: 3 H0617: 7, L0438: 6, L0794: 3, L0766: 3, L0791: 3, H0618: 2, S0344: 2, L0769: 2, L0662: 2, L0758: 2, L0662: 1, H0733: 1, H0052: 1, H0178: 1, H0023: 1, H0066: 1, H0178: 1, H0023: 1, H066: 1, H0135: 1, T0004: 1, H0509: 1, S0144: 1, L0803: 1, L0744: 1, L0747: 1, L0744: 1, L0779: 1, L0731: 1, S0436: 1, S0194: 1 and H0542: 1.	AR055: 14, AR060: 13,
		1457 Leu-3 to Gln-18.
	1456	1457
	46 - 354	225 -
•	21	52
	574924	575287
	HTLA185	ннРСО38
	14	42

	68-86, 89- 108, 40-56	63-84	53-75, 92- 112, 25-45
AR089: 12, AR096: 10, AR052: 8, AR033: 8, AR061: 7, AR053: 5, AR104: 0, AR039: 0 L0756: 2, H0051: 1, S0380: 1, L0748: 1 and L0753: 1.	AR033: 4, AR089: 3, AR060: 3, AR104: 1, AR061: 1, AR053: 1, AR096: 1, AR039: 0, AR052: 0, AR055: 0 L0748: 5, H0444: 2, H0402: 1, L0367: 1 and S0052: 1.	AR060: 10, AR089: 8, AR033: 7, AR104: 2, AR061: 1, AR053: 1, AR096: 1, AR055: 1, AR039: 0 H0123: 2 and H0318: 1.	AR033: 5, AR052: 4, AR089: 4, AR053: 4, AR055: 3, AR060: 2, AR096: 2, AR061: 2, AR039: 1 L0438: 4, L0803: 3, H0169: 2, L0526: 2, H0657: 1, S0408: 1, H0421: 1,
	Gln-22 to Gly-28, Thr-109 to Gly-114, Phe-117 to Arg-124.	1459 Gly-35 to Gln-41, Phe-51 to Lys-57.	
	1458	1459	1460
530	229 - 639	252 - 551	73 - 426
	53	54	55
	<i>576</i> 739	578925	581501
	HNGER82	HBJLU13	HCFDCS5
	8	4	45

H0050: 1, 50370: 1, L0637: 1, L0646: 1, L0800: 1, 1, L0646: 1, L0800: 1, 1, L0651: 1, L0607: 1, L0652: 1, L0665: 1, 1, 50328: 1, H0659: 1, H0651: 1, 50328: 1, H0659: 1, 1, 50328: 1, H0636: 1, 1, 50328: 1, H0436: 1, 1, 1, 2, 2, AR098: 2, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1	WO 01/90304		PC1/U	201/10
H0050: 1, S0370: 1, L0637: 1, L0646: 1, L0800: 1, 1, L0646: 1, L0607: 1, 1, L0658: 1, 1, L0772: 1, L0722: 1, S0242: 1, S0328: 1, H0436: 1, 1, S0328: 1, H0436: 1, 1, L0777: 1, L0722: 1, S0242: 1, L0777: 1, L0722: 1, S0242: 1, Lys-127 to Pro-132. AR059: 2, AR096: 1, 1, Lys-127 to Pro-132. AR059: 1, AR096: 1, 1, Lys-127 to Pro-132. AR059: 1, AR096: 1, 1, Lys-127 to Pro-132. AR059: 1, H0063: 1, 1, L0763: 1, L0794: 1, 1, L073: 1, L0787: 1, 1, L073: 1, L0787: 1, 1, L073: 1, and S0276: 1, 1, L073: 1, and S0276: 1, 1, L073: 1, and S0276: 1, 1, L0748: 2, AR099: 8, 1, L0748: 2, and H0575: 1, 1, L0748: 2, and H0578: 1, 1,		83-101, 62-78	66-82	57-86
H0050: 1, S0370: 1, L0637: 1, L0646: 1, L0800: 1, L0662: 1, L0766: 1, L0607: 1, L0659: 1, L0665: 1, L0352: 1, H0659: 1, H0651: 1, L0352: 1, H0659: 1, H0651: 1, L0352: 1, H0659: 1, H0651: 1, L0352: 1, H0659: 1, L0665: 1, L0352: 1, H0659: 1, L0665: 1, L0352: 1, H0659: 1, L0665: 1, L0777: 1, L0752: 1, S0242: 1, L0777: 1, L0752: 1, S0242: 1, L0777: 1, L0752: 1, L0769: 1, L0773: 1, L0763: 1, L0794: 3, L0766: 2, L0788: 2, S0192: 2, H0012: 3, L0794: 3, L0766: 2, L0788: 2, S0192: 2, H0013: 1, L0794: 1, L0732: 1, L0794: 1, L0732: 1, L0794: 1, L0733: 1 and S0276: 1, L0731: 1 and S0276: 1, L0733: 1 and S0276: 1, L0733: 1 and S0276: 1, L0733: 1 and S0276: 1, L0748: 2 and H0575: 1, L0749: 2 and H0575: 1, L0748: 2 a				102200, 106100,
56 178 - 1461 Leu-12 to Gly-18, 1 Tyr-27 to Glu-34, 1 Lys-127 to Pro-132. 1 Lys-127 to Pro-132. 2				11q13
56 178 - 1461 591 57 13 - 330 1462 58 660 1463	H0050: 1, S0370: 1, L0637: 1, L0646: 1, L0800: 1, L0662: 1, L0766: 1, L0607: 1, L0659: 1, L0659: 1, H0651: 1, S0328: 1, H0436: 1, L0777: 1, L0752: 1, S0242: 1 and H0422: 1.	AR053: 2, AR089: 2, AR060: 2, AR096: 1, AR055: 1, AR061: 1, AR039: 0, AR052: 0 H0012: 3, L0794: 3, L0766: 2, L0788: 2, S0192: 2, H0618: 1, H0015: 1, H0073: 1, T0023: 1, H0063: 1, L0763: 1, L0787: 1, L0532: 1, S3012: 1, S0027: 1, L0747: 1, L0750: 1, L0731: 1 and S0276: 1.	AR055: 15, AR039: 15, AR033: 13, AR104: 12, AR061: 12, AR053: 10, AR089: 9, AR060: 9, AR052: 8, AR096: 8 L0748: 2 and H0575: 1.	AR033: 4, AR089: 3, AR096: 2, AR061: 2,
56 178 - 591 591 57 13 - 330	•	Leu-12 to Gly-18, Tyr-27 to Glu-34, Lys-127 to Pro-132.	Lys-2 to Ser-10, Gln-20 to Leu-25, Val-29 to Arg-53.	1463 Gly-2 to Leu-7, Pro-11 to Leu-26,
57 57		1461	1462	1463
		178 - 591	13 - 330	660 - 331
810 520		56	57	58
586/		586810	587520	589293
		HFKCT25	HAPOW05	HCUFP05
64 74 84		8	47	48

VO 01/90304 P	CT/US01/1645
	56-72, 1- 17, 76-92
131100, 131100, 131100, 131780, 147050, 164009, 164009, 168461, 188461, 180721, 180721, 193235, 209901, 232600, 259770, 600045, 601884	Xq22.3-q23 300046, 300067, 300067, 300121,
	Xq22.3-q2
AR060: 2, AR055: 2, AR104: 1, AR039: 0, AR052: 0, AR053: 0 L0769: 9, L0752: 6, L0747: 5, L0759: 5, L0764: 4, L0806: 4, L0758: 4, H0649: 3, L0770: 3, L0783: 3, L0750: 3, S0408: 2, H0687: 2, L0771: 2, L0662: 2, L0794: 2, L0775: 2, L0805: 2, L0776: 2, L0809: 2, L0795: 2, L0776: 2, L0809: 1, S0134: 1, H0664: 1, H0402: 1, H0664: 1, H0402: 1, H0664: 1, H0012: 1, H0014: 1, H0688: 1, L0779: 1, L0761: 1, L0772: 1, L0800: 1, L0761: 1, L0772: 1, L0800: 1, L0761: 1, L0800: 1, L0773: 1, L0659: 1, L0768: 1, L0766: 1, L0659: 1, L0778: 1, L0659: 1, L0778: 1, L0659: 1, L0778: 1, L0786: 1, L0777: 1 and	L0731: 1. AR096: 16, AR053: 14, AR055: 14, AR052: 11, AR060: 8, AR089: 8, AR033: 8, AR104: 7,
Gly-28 to Ala-40, Arg-51 to Pro-58, Asp-92 to Leu-97.	Gln-28 to Pro-41, Lys-94 to Pro-108.
	1464
•	161 - 514
	59
	597069
	HE8CX53
·	<u> </u>

	PC1/USU1/10
50, 4-	32 66, 16-
7.24 7.24	32 47-6
162400, 227645, 229700, 278700, 601309, 601309, 602014, 602088	129010, 154545, 164761, 164761, 164761, 188550, 601386,
	10q11.2- q21.1
AR104: 19, AR033: 15, AR039: 5, AR061: 5, AR053: 5, AR096: 5, AR052: 4, AR055: 4, AR089: 4, AR060: 3 H0052: 3, S0001: 2, S0222: 1, H0194: 1, L0157: 1, L0369: 1, L0769: 1, L0767: 1, L0794: 1, H0144: 1 and L0438: 1.	AR053: 1, AR055: 1, AR096: 1, AR089: 1, AR061: 0, AR060: 0, AR104: 0, AR033: 0, AR052: 0, AR039: 0 S0184: 26 and S0186: 8.
	Val-40 to Tyr-45.
1465	1466
65 - 508	151 - 498
09	61
597213	597832
HCENB31	H7TMESS
0	51
	597213 60 65 - 508 1465 AR039: 5, AR061: 5, AR061: 5, AR056: 5, AR056: 5, AR056: 5, AR056: 5, AR056: 4, AR055: 4, AR055: 4, AR055: 4, AR089: 4, AR060: 3 H0052: 3, S0001: 2, S0222: 1, H0194: 1, L0157: L0169: 1, L0169

80-111	<i>21</i> -09	100-116, 14-30
AR060: 18, AR055: 16, AR104: 14, AR061: 14, AR033: 11, AR089: 11, AR039: 7, AR096: 6, AR053: 5, AR052: 4 L0439: 13, L0438: 6, H0052: 3, H0009: 2, L0769: 2, L0794: 2, L0741: 2, H0229: 1, H0572: 1, H0569: 1, L0770: 1, L0796: 1, L5566: 1, L0805: 1, L0789:	AR096: 5, AR055: 3, AR039: 2, AR061: 2, AR033: 2, AR089: 2, AR104: 2, AR052: 2, AR060: 1, AR053: 1 S0038: 1	AR033: 10, AR055: 9, AR104: 6, AR052: 5, AR089: 5, AR096: 5, AR060: 5, AR061: 4, AR053: 4, AR039: 2 L0757: 13, L0759: 7, L0747: 6, T0010: 5, L0748: 5, L0770: 4, L0764: 4, L0750: 4, H0031: 3, L0438: 3, L0756: 3, L0758: 3, H0013: 2, S0010: 2, H0135:
1467 Ser-15 to His-22, A Pro-46 to Pro-52, A Gly-63 to Ser-69, A Arg-111 to Ser-116, A Pro-121 to Asn-129, A Ala-136 to Gly-145. H H L L L L L L	4444	Thr-8 to Glu-13, A Thr-89 to Leu-96. A A A A B A A A A A A A A A A A A A A A
1467	1468	1469
75 - 539	18 - 362	122 - 472
29	ಜ	2
600734	610609	613240
HDHMA49 600734	HBXBG68	HGBFCS3
22	23	22

			1 01/0501/10
	39		21-42, 44- 66
	107-139	61-97	21.42
		Ψ	21
•			
	:7:		
1, H069 1, L074 L078 L058 1,	23, 44, 4, 1074	Q4.00.00 '	4,6,6,4
543: 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,	8, AR060: 4, AR089: 4, AR096: 3, AR052: 2, AR052: 7, H0644: 4, 2, L0748: 1, I	961: 996: 952: 953: 71: 3	60: 65: 55:
1. 1.05 0665 1. 1.07 0751 0596 0596 0666 0666 0751 0751 0751 0751	8, AR060: 4, AR089: 4, AR096: 3, AR053: 2, AR052: 7, H0644: 4 4, L0748: 1,	7, AR061: 5, AR096: 4, AR052: 3, AR053: 2, AR039: 4, H0271: 3 and L0599:	7, AR060: 3, AR089: 3, AR061: 2, AR055:
29: 1 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1	8, 4, 4, 3, 2, 1, 1054, 1	7, 2, 4, 5, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,	 6, w, w, c ₁
11, L0809: 1, L0543: 1, L0647: 1, L0665: 1, H0698: 1, S0374: 1, H0520: 1, H0689: 1, H0682: 1, H0521: 1, S0028: 1, L0742: 1, L0740: 1, L0751: 1, L0749: 1, L0752: 1, S0031: 1, H0445: 1, L0596: 1, L0588: 1, L0593: 1, L0603: 1, H0667: 1 and H0542: 1.	AR055: 8, AR060: 5, AR061: 4, AR089: 4, AR033: 4, AR096: 4, AR039: 3, AR053: 3, AR104: 2, AR052: 2 L0754: 7, H0644: 4, H0031: 2, L0748: 1, L0747: 1 and H0543: 1.	AR055: 7, AR061: 6 AR060: 5, AR096: 4 AR033: 4, AR052: 3 AR089: 3, AR053: 3 AR104: 2, AR039: 2 H0575: 4, H0271: 3,	AR033: AR096: AR053: AR052:
<u> </u>	AAAAAHHI		
· .	97.	26, 47, 60, 9-127	20, -102
	Pro	Glu Ser- Thr o Tr	Ala-
	91 to	15 to 33 to 53 to 119 t	10 to 82 to
	Thr.	Ala-15 to Glu-26, Lys-33 to Ser-47, Cys-53 to Thr-60, Cys-119 to Trp-127.	Thr-10 to Ala-20, Asp-82 to Asn-102.
	1470 Thr-91 to Pro-97.	1471	1472
	17		14
-	336 -	5 - 478	129 - 434
		v	,
	99	99	<i>L</i> 9
	734	77.	69
	613734	613777	614169
		(53	302
	HPMCK47	HAPNX53	HOFAE02
	岜	扭	<u>н</u>
	55	26	

	143-159	78-96
2, \$0410: 2: 2, 1, H0692: 2: 1, 2: 1, 3: 1, 1, \$0010: 5: 1, 1, \$0010: 5: 1, 1, \$0010: 5: 1, 1, \$0010: 5: 1, 1, \$0010: 5: 1,	22: 1. 24: 4, 33: 3, 34: 1, 34: 1, 34: 1, 35: 1, 36	4
AR104: 1, AR039: 0 S0136: 7, S0356: 2, S0410: 2, H0486: 2, H0672: 2, H0170: 1, H0657: 1, H0692: 1, H0254: 1, H0402: 1, H0305: 1, S0358: 1, H0619: 1, L0717: 1, H0406: 1, H0415: 1, H0599: 1, S0010: 1, T0115: 1, H0545: 1, S0051: 1, H0617: 1, H0264: 1, H0100: 1, L0659: 1, L0789: 1, L0665: 1, H0519: 1, H0414: 1, S0406: 1.	AR052: 1 and H0352: 1. AR055: 5, AR033: 5, AR060: 4, AR104: 4, AR052: 3, AR089: 3, AR056: 2, AR039: 1 L0439: 6, L0438: 3, L0809: 2, L0748: 2, H0583: 1, S0001: 1, T0010: 1, L0456: 1, H0598: 1, L0761: 1, L0783: 1, S0028: 1, L0749: 1, L0756: 1, S0458: 1 and H0352: 1.	AR039: 6, AR053: AR052: 3, AR033: AR096: 3, AR055:
AR104 S0136 2, H04 1, H02 1, L07 1, L07 1, T01 S0051: 1, H04 1, H04 1, H04 1, H04	H0422 AR055 AR055 AR052 AR096 L0439 1, S000 1, S000 1, L074 11 and I	
,		1474 Ser-19 to Val-24, Pro-35 to Asn-42, Pro-44 to Gly-59,
	1473	1474
	16 - 525	234 - 593
	89	69
	614801	615231
	HSLIQ83	HNTMD04 615231
	88	59

	92-111, 45-61	60-76	48-81, 126-156, 89-115, 21-38, 1- 17, 180-
AR089: 3, AR060: 2, AR061: 2, AR104: 2 L0755: 3, H0521: 2, L0754: 2, L0747: 2, S0003: 1, L0369: 1, L0667: 1, L0659: 1, L0667: 1, L0663: 1, L0664: 1, H0520: 1, H0518: 1, S0152: 1, S0404: 1, H0436: 1, L0748: 1 and H0423: 1.	AR104: 20, AR096: 11, AR089: 8, AR033: 7, AR052: 5, AR060: 5, AR053: 5, AR039: 4, AR055: 2, AR061: 1 H0599: 1, H0555: 1 and S0390: 1.	AR055: 12, AR089: 8, AR033: 8, AR061: 7, AR060: 7, AR053: 5, AR052: 5, AR096: 4, AR039: 1, AR104: 0 L0758: 2, H0339: 1, L0664: 1 and L0731: 1.	AR096: 1, AR089: 1, AR104: 1, AR033: 0, AR052: 0, AR061: 0, AR039: 0, AR060: 0, AR055: 0, AR053: 0
Gly-96 to Gly-101.	1475 Thr-17 to Ser-28, Ser-39 to Gly-45.	1476 Arg-5 to Glu-10.	Glu-121 to Asp-128.
	1475	1476	1477
	47 - 379	345 - 680	110 - 748
	92	71	72
	616154	616652	618715
	HRABY48	HDDAA17	HTRAC41
	09	19	79

M () () 1/30.	704		PC 1/USU1/164
196, 161- 177	52-68, 26- 42	46-64, 130-146	81-99, 34- 50
		·	
0: 2, 8: 1, H0735: S0028: 1.	055: 11, 053: 10, 60: 9, 89: 9, 61: 6	33: 7, 60: 6, 61: 4, 39: 0	39: 1, 04: 1, 96: 1, 61: 1, 62: 0 3: 2, 1: 1, S0354: 60: 1, 71: 1, 29: 1,
S0001: 2, H0730: 2, L0581: 2, H0713: 1, H0735: 1, H0164: 1 and S0028: 1.	AR039: 25, AR055: 11 AR033: 10, AR053: 10 AR096: 9, AR060: 9, AR052: 9, AR089: 9, AR104: 8, AR061: 6 S0003: 1, L0498: 1 and L0599: 1.	AR055: 10, AR052: 9, AR053: 8, AR033: 7, AR089: 6, AR060: 6, AR096: 4, AR061: 4, AR104: 1, AR039: 0 H0441: 1, H0409: 1 and S0344: 1.	AR060: 2, AR039: 1, AR053: 1, AR104: 1, AR033: 1, AR066: 1, AR089: 1, AR061: 1, AR055: 0, AR052: 0 L0755: 3, S0003: 2, H0521: 2, S0470: 1, S0354: 1, S0444: 1, S0360: 1, S0046: 1, H0574: 1, S0010: 1, H0046: 1, L0471: 1, H0051: 1, H0553: 1, H0646: 1, S0210: 1, H0529: 1,
	8.	Arg-78 to Glu-84, Leu-94 to Trp-102, Lys-113 to Thr-118.	
	1478	1479	1480
	57 - 407	1 - 519	221 - 670
	73	47	75
	619875	620219	625334
	HOSCV06	HMCHS27	HEMFC09
		2	\$9

	<i>S1-73</i>	79-95
10658: 0192: 3: 1.	3, 2, 1, 1, 10624: 10644: 10538: 10435: and	0,0,1,2
1, H0539: 1, H0659: 1, H0658: 1, H0539: 1, H0436: 1, H0758: 1, L0599: 1, S0192: 1, S0276: 1 and H0423: 1.	AR053: 3, AR052: 3, AR096: 2, AR039: 2, AR056: 1, AR089: 2, AR060: 1, AR061: 1, AR104: 1, AR061: 1, AR104: 1, AR039: 0 L0748: 4, L0749: 3, H0529: 2, L0439: 2, H0624: 1, H0638: 1, H0649: 1, H0651: 1, H0644: 1, H0690: 1, H0646: 1, L0500: 1, L0646: 1, L0794: 1, L0666: 1, L0664: 1, L0666: 1, L0664: 1, H0696: 1, R0644: 1, L0666: 1, L0664: 1, L0790: 1, L0794: 1, L0790:	2, AR055: 1, AR104: 0, AR033: 0, AR052:
L0662: 1, 1 1, H0539: L0758: 1, 1 1, S0276: 1		AR096: 2, AR055: AR089: 1, AR104: AR061: 0, AR033: AR060: 0, AR052:
	1481 Glu-90 to Asn-95, Arg-101 to Lys-108.	Ala-25 to Phe-44.
	1481	1482
	25 - 798	272 - 571
	92	77
	625432	625517
	HNTRJ16	HKAEJ09
	99	19

WO 01/90304			PC1/US01/164
	56-72, 18- 34	46-64	50-70, 20- 42
	4 × ×		
AR039: 0, AR053: 0 H0083: 1, H0494: 1, L0776: 1, L0744: 1 and L0777: 1.	AR033: 7, AR089: 5, AR060: 4, AR039: 3, AR055: 3, AR053: 3, AR061: 3, AR052: 3, AR096: 2, AR104: 1 H0265: 2, H0431: 2, H0486: 2, H0004: 2, H0624: 1, H0716: 1, H0657: 1, S0222: 1, H0083: 1, S0214: 1, H0628: 1, L0809: 1, H0547: 1, L0748: 1, L0439: 1, L0749: 1, L0485: 1 and H0543: 1.	AR096: 2, AR089: 1, AR039: 1, AR033: 1, AR061: 1, AR104: 0, AR060: 0, AR052: 0, AR055: 0	AR055: 6, AR061: 3, AR052: 3, AR060: 3, AR096: 3, AR033: 3, AR053: 2, AR089: 2, AR039: 2, AR104: 1 H0040: 3
	1483 Tyr-49 to Arg-55.	Pro-13 to His-18, Pro-20 to Lys-27, Ala-29 to Pro-47, Lys-69 to Arg-75, Ser-77 to Ser-85.	1485 Phe-42 to Tyr-50.
	1483	1484	1485
	22 - 414	92 - 517	44 - 361
	82	61	08
	9722566	625622	626178
	HKMMS65 625566	HNHGE09	HTTCT34
	89	99	70

WO 01/90304	PCT/US01/16450
7-27, 114- 130, 88- 104, 31- 47, 61-77	86-105, 12-29, 55- 71
* * * * * *	8 8 8 3 8
1486 Arg-133 to Lys-145. AR033: 164, AR055: 129, AR061: 128, AR060: 117, AR089: 90, AR039: 62, AR089: 90, AR039: 62, AR0852: 41, AR104: 40, AR053: 30, AR096: 23 L0805: 9, S0010: 2, S6024: 1, S0134: 1, H0733: 1, S0132: 1, H0592: 1, T0048: 1, S0474: 1, S049: 1, H0196: 1, H0052: 1, H0673: 1, S0450: 1, L0776: 1, L0809: 1, H0723: 1, S3012: 1, R3014: 1, L0748: 1, L0758: 1 and L0599: 1.	AR096: 35, AR089: 31, AR104: 25, AR060: 17, AR033: 16, AR052: 15, AR039: 14, AR053: 13, AR055: 10, AR061: 6 H0556: 3, H0208: 3, H056: 3, L0471: 3, H0179: 3, H0644: 3, S0344: 3, H0521: 3, L0439: 3, S0420: 2, S0360: 2, H0619: 2, H0599: 2, H0564: 2, H0280: 2, S0210: 2, H0547: 2, H0658: 2, L0750: 2, L0731: 2, L0588: 2, L0604: 2, H0543: 2, H0265: 1, T0002:
Arg-133 to Lys-145. A	дада шененен
1486	1487
751 - 1185	354 - 722
18	8
637714	638175
71 HBIAS14 637714	HLHSC60
17	27

VO 01/90304 PC 1/050	71/1043
	136-153, 18-34
1, H0140: 1, S0114: 1, H0341: 1, H0662: 1, H0306: 1, S0418: 1, S0401: 1, H0580: 1, L0717: 1, H0549: 1, H0645: 1, H0532: 1, H0549: 1, H0645: 1, H0652: 1, H0652: 1, H0659: 1, H0632: 1, H0657: 1, H0630: 1, H0630: 1, H0630: 1, H0630: 1, H0631: 1, L0431: 1, L0631: 1, L0631: 1, L0631: 1, L0631: 1, H0651: 1, H0653: 1, L0653: 1, L0789: 1, L0663: 1, L0773: 1, H0539: 1, L0748: 1, L0773: 1, H0539: 1, L0748: 1, L0777: 1, L0753: 1, H0642: 1, H06	AR055: 17, AR033: 17, AR052: 13, AR061: 13,
	1488 Gln-7 to Arg-12, Pro-69 to Glu-76,
	1488
	427 - 894
	83
	638229
	H6ESA95
	73

WO 01/90304		PC 1/USU1/16
	78-112, 1- 36, 49-77, 213-232, 105-121, 29-45	191-207, 139-155
·		
H0691: 1, H0435: 1, H0436: 1, H0478: 1, L0750: 1, L0731: 1, L0757: 1, H0445: 1, L0601: 1, H0653: 1, H0543: 1 and S0424: 1.	Lys-126 to Phe-135, AR104: 504, AR061: 378, A8n-153 to Ala-168, AR030: 236, AR055: 296, Thr-185 to Val-196. AR039: 203, AR039: 173, AR089: 171, AR052: 122, AR089: 171, AR052: 122, AR080: 171, AR096: 94 S0358: 11, H0494: 9, S0358: 11, H0494: 9, S0354: 7, S0442: 6, H0593: 6, S0444: 5, S0408: 3, H0370: 3, H0616: 2, H0639: 3, S0434: 3, H0616: 2, H0639: 3, E1, H0648: 1, S0376: 1, S0360: 1, H0648: 1, S0376: 1, S0360: 1, H0648: 1, S0440: 1, H0673: 1, S0440: 1, H0673: 1, L0809: 1, H0689: 1, H0672: 1, S0044: 1, S0446: 1, H0506: 1 and L0600: 1.	AR039: 2, AR052: 1, AR033: 1, AR055: 1, AR089: 1, AR104: 1, AR096: 1, AR061: 1,
4 - 1	Lys-126 to Phe-135, Asn-153 to Ala-168, Thr-185 to Val-196. Asn-196. Asn-19	Lys-5 to Thr-16, Thr-23 to His-28, Gly-111 to Leu-121, Pro-128 to Ile-137.
	1489	1490
	- 888 888	259 - 996
	<u>\$</u>	85
	638339	638553
	HKMAA36	HLTFA02
	47	75

WU 01/90304		rc	1/(JOU	1/1	645
	180-210,	257-282,	326-349,	116-134,	308-325,	12-28
AR060: 1, AR053: 0 L0747: 6, L0766: 4, L0749: 4, L0362: 4, H0046: 3, L0666: 3, S0126: 3, S0132: 2, H0013: 2, L0758: 2, L0596: 2, H0624: 1, H0341: 1, S0001: 1, S0360: 1, S0408: 1, S0278: 1, H0370: 1, H014: 1, H0083: 1, H0553: 1, H0606: 1, H0561: 1, H0638: 1, H0616: 1, L0520: 1, L0641: 1, L0764: 1, L0805: 1, L0526: 1, L0664: 1, H0702: 1, H0559: 1, H0658: 1, H0660: 1, H0659: 1, H0658: 1, H0660: 1, H0659: 1, H0658: 1, H0660: 1, H0659: 1, H0658: 1, H0660: 1, L0777: 1, L0755: 1, L0731: 1, L0759: 1, L0755: 1, L0731: 1, L0759: 1, L0755: 1, L0731: 1, L0759: 1, H0422: 1 and S0452: 1.	AR060:	AR089:	AR053:	rp-110, AR055: 1, AR061: 1,	AR104:	H0539:
	1491 Leu-50 to Lys-58,	Lys-64 to Leu-71,	His-89 to Thr-94,	Pro-102 to Trp-110,	Tyr-162 to Cys-169,	Asp-367 to Ala-377.
	86 48 -	1193				
	HISBE12 645267				-	
	H 9/					

WO 01/90304		PC 1/USU1/10
	19-51, 100-116, 120-136, 41-57	117-133
H0039: 2, H0553: 2, H0090: 2, L0750: 2, L0605: 2, S0282: 1, H0431: 1, H0036: 1, H0421: 1, H0196: 1, T0003: 1, S6028: 1, H0252: 1, H0031: 1, H0111: 1, H0591: 1, H0412: 1, T0068: 1, S0044: 1, L0752: 1, H0445: 1 and L0581: 1.	AR104: 44, AR033: 31, AR051: 18, AR060: 15, AR055: 14, AR039: 12, AR089: 12, AR096: 10, AR053: 9, AR052: 6 S0007: 3, H0038: 2, S0344: 2, L0750: 2, T0002: 1, H0125: 1, S0420: 1, S0358: 1, S046: 1, H0411: 1, S0278: 1, H0085: 1, H0545: 1, H0031: 1, H0182: 1, H0646: 1, H0134: 1, S0031: 1, L0591: 1, H0423: 1 and H0422: 1.	AR053: 51, AR052: 50, AR089: 25, AR055: 25, AR033: 17, AR061: 14, AR060: 12, AR096: 12, AR104: 1, AR039: 0
	Glu-9 to Arg-15, Pro-71 to Lys-79.	1493 Met-1 to Val-12.
	1492	1493
	62 - 520	158 - 646
	28	88
	645268	655007
	HEBAE43	HSBBC07
	F	78

78-95, 1- 17, 52-68	89-107	23-68, 23-41	131-151, 64-80, 34-
AR055: 10, AR060: 9, AR096: 8, AR053: 8, AR039: 8, AR089: 7, AR104: 7, AR061: 6, AR052: 5, AR033: 5 H0131: 2, S0002: 2, H0664: 1, H0586: 1, H0574: 1, H0563: 1, H0028: 1 and S0428: 1.	AR052: 30, AR053: 25, AR096: 23, AR055: 18, AR089: 16, AR060: 12, AR033: 10, AR061: 8, AR104: 6, AR039: 5 L0756: 2, H0170: 1, H0441: 1, S0051: 1, T0010: 1, H0436: 1 and L0779: 1.	AR055: 44, AR039: 39, AR053: 24, AR033: 20, AR052: 18, AR089: 17, AR104: 16, AR096: 14, AR060: 13, AR061: 12 L0748: 5, L0157: 3, L0777: 2, H0549: 1, H0617: 1, L0638: 1, L0774: 1, L075: 1, H0144: 1 and L075: 1.	AR039: 8, AR033: 5, AR053: 5, AR096: 4,
18 - 329 1494 Pro-16 to Lys-21.	1495 Val-7 to Met-23, Leu-41 to Lys-46.	Asp-14 to Leu-22.	1497 Gln-18 to Tyr-24, Gln-94 to Glu-100.
- 329 1494	18	51 - 395 1496	228 - 1497 722
89	90 344 -	91 51	22 7.
0655590	656211	656288	656815
HI.2AE73	HE20057	HEEAR13	HFIYL13
79	08	81	82

VO 01/90304	PCT/US01/1645
20	46-62
AR052: 4, AR104: 4, AR089: 4, AR055: 3, AR060: 3, AR061: 3 L0766: 3, H0413: 2, L0794: 2, H0659: 2, H0591: 1, T0042: 1, H0494: 1, L0769: 1, L0667: 1, L0800: 1, L062: 1, L0766: 1, H0658: 1, L0748: 1, L0755: 1, L0731: 1, L0758: 1, H0444: 1, S0242: 1 and	AR039: 34, AR053: 20, AR096: 17, AR033: 16, AR052: 16, AR104: 15, AR089: 14, AR055: 11, AR060: 11, AR061: 8 L0754: 9, L0780: 3, L0755: 3, L0591: 3, S0196: 3, H0255: 2, H0306: 2, H0041: 2, H0553: 2, H0674: 2, H0521: 2, L0748: 2, L0779: 2, L0752: 2, L0753: 2, H0445: 2, L0589: 2, S0298: 1, H0346: 1, S0360: 1, S0408: 1, H0549: 1, H0550: 1, H0485: 1, H0428: 11, H0628: 1, L0369: 1, S0142: 1, L0369: 1, L0769:
	TO HOLD THE SECOND
	1498
	- 542 542
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84 HATDW31 659283 94 579- 1499	10 01/20304		1 C 1 / C 50 1 / 10
HATDW51 659283 94 579 - 1499 HATDW69 659380 95 22 - 444 1500 Phe-68 to Ser-77, Lys-79 to Thr-90, Cys-107 to Leu-114, Pro-124 to Asn-133.		50, 75-91 50, 75-91	47-64
HATDW51 659283 94 579 - 1499 HATDW69 659380 95 22 - 444 1500 Phe-68 to Ser-77, Lys-79 to Thr-90, Cys-107 to Leu-114, Pro-124 to Asn-133.	,		
HATDW51 659283 94 579 - 1499 HATDW69 659380 95 22 - 444 1500 Phe-68 to Ser-77, Lys-79 to Thr-90, Cys-107 to Leu-114, Pro-124 to Asn-133.			
HATDW51 659283 94 579 - 1499 HATDW69 659380 95 22 - 444 1500 Phe-68 to Ser-77, Lys-79 to Thr-90, Cys-107 to Leu-114, Pro-124 to Asn-133.	803: 1, L0782: 1, L0791: L0532: 1, L0777: 1, 444: 1, L0596: 1, S0026: nd H0653: 1.	1033: 7, AR053: 4, 1055: 4, AR052: 3, 1096: 3, AR089: 3, 1060: 3, AR061: 2, 1039: 2, AR104: 1 10766: 4, L0758: 4, 10745: 2, L0756: 2, 10771: 1, L0648: 1, L0794: 1, L0774: 1, 1, L0439: 1, L0747: 1 and S0412: 1.	AR052: 29, AR053: 25, AR096: 23, AR089: 12, AR055: 8, AR033: 6, AR104: 0, AR039: 0 L0805: 25, L0157: 7, L0776: 7, S0474: 5, L0731: 5, H0457: 4, L0748: 4, L0747: 4, S0278: 3, H0538: 3, S0404: 3, S0476: 2, H0619: 2, H0009: 2, H0529:
HATDW51 659283 94 579- 1499 878 HDPWQ69 659380 95 22 - 444 1500	1, 10 HIGH	######################################	14, 21, 33.
HATDW51 659283 94 HDPWQ69 659380 95		1499	
HATDW51 659283 HDPWQ69 659380		878	22 - 444
		4	8
		659283	659380
		HATDW51	нDPWQ69
<u> </u>			28

	252-268, 133-149, 106-122
· · · · · · · · · · · · · · · · · · ·	
2, L0662: 2, L0803: 2, L0774: 2, L0439: 2, L0751: 2, H0170: 1, H0713: 1, H0716: 1, H0295: 1, H0341: 1, S0001: 1, H0663: 1, H0306: 1, H0402: 1, S0418: 1, L0005: 1, S0222: 1, H0587: 1, T0060: 1, H0427: 1, H0575: 1, T0048: 1, H0678: 1, L0648: 1, L0648: 1, L0648: 1, L0678: 1, L0667: 1, L0698: 1, L0770: 1, L0689: 1, L0775: 1, L0667: 1, L0673: 1, L0775: 1, L0663: 1, H0670: 1, L0799: 1, L0663: 1, H0670: 1, L0799: 1, L0663: 1, H0670: 1, S0380: 1, H0521: 1, H0521: 1, H0521: 1, H0521: 1, L0777: 1, L07	L0758: 1, S0194: 1, H0423: 1 and H0352: 1. AR053: 1, AR055: 1, AR060: 1, AR033: 1, AR096: 0, AR061: 0,
	Pro-8 to Ala-14, Glu-68 to Gln-75, Gln-80 to Glu-85,
	1501
	231 - 1058
	96
	659801
	HNTBM67 659801
	魠

	58-75
1, H0662: 1, S0418: 1, S0376: 1, S0045: 1, S0046: 1, H0411: 1, H0369: 1, H0550: 1, H0438: 1, H0602: 1, T0040: 1, H0013: 1, H0427: 1, S0280: 1, H0590: 1, H0390: 1, S0474: 1, H0178: 1, H0562: 1, H0178: 1, H0562: 1, H0178: 1, H0562: 1, H0178: 1, H0562: 1, H0613: 1, H0373: 1, H0563: 1, H0613: 1, H0553: 1, H0563: 1, L0564: 1, L0773: 1, L0773: 1, L0564: 1, L0773: 1, L0569: 1, L0773: 1, L050: 1, L0566: 1, L0773: 1, L0809: 1, S0370: 1, H0659: 1, S0330: 1, H0659: 1, S0328: 1, S0330: 1, H0539: 1, S0328: 1, L0755: 1, L0753: 1, H0657: 1, S0436: 1, H0667: S0436: 1, H0667:	1 and S0242: 1. AR055: 31, AR060: 21,
·	Met-1 to Lys-7,
	1502
	37 - 537
	26
	660532
	HAIDY03
	87

V 0.17.0001	
	44-72, 69-
AR033: 20, AR061: 15, AR089: 13, AR053: 12, AR096: 6, AR039: 4 L0766: 5, L0803: 3, L0748: 3, L0740: 3, L0758: 3, S0408: 2, H0032: 2, H0124: 2, L0771: 2, L0809: 2, L0655: 2, S0330: 2, L0750: 2, L0756: 2, L0731: 2, L0759: 2, H0254: 1, H0638: 1, S0420: 1, S0358: 1, S0132: 1, H0013: 1, S0010: 1, H0563: 1, H0591: 1, H0416: 1, H0687: 1, S0003: 1, H0507: 1, H0538: 1, L0769: 1, L0796: 1, L0769: 1, L0796: 1, L0769: 1, L0796: 1, L076: 1, L0643: 1, L078: 1, L0794: 1, L0664: 1, H0144: 1, H0519: 1, H0690: 1, H0558: 1, H0672: 1, H0518: 1, H0696: 1, S0044: 1, L0439: 1, L0747: 1, L0752: 1, S0192: L0747: 1, L0752: 1, S0192:	53: 3,
AR033: 20, AR061: 15 AR089: 13, AR053: 12 AR089: 13, AR053: 12 AR096: 6, AR039: 4 L0766: 5, L0803: 3, L0748: 3, L0740: 3, L07 3, S0408: 2, H0032: 2, H0124: 2, L0771: 2, L07 2, L0655: 2, S0330: 2, L0750: 2, L0756: 2, L07 2, L0655: 2, S0330: 2, L0750: 2, L0756: 2, L07 1, S0132: 1, H0013: 1, S0010: 1, H0563: 1, H0 1, H0416: 1, H0687: 1, S0003: 1, H0328: 1, H0 1, H0413: 1, H0207: 1, L0763: 1, L0769: 1, L0805: 1, L0776: 1, L04 1, L0783: 1, H0144: 1, H0 1, L0783: 1, H0518: 1, H0 1, S0044: 1, L0732: 1, S01 1, s0044: 1, L0732: 1, S01 1, sund H0422: 1.	AR096: 3, AR053:
Pro-9 to Ser-19, Pro-30 to Ser-38, Arg-89 to Glu-95, Leu-105 to Trp-113, Lys-124 to Thr-129.	Thr-107 to Asn-114.
Pro-9 to Ser-19, Pro-30 to Ser-38, Arg-89 to Glu-95, Leu-105 to Trp-1; Lys-124 to Thr-12	
	1503
	376 - 35
	86
	661436
	HDPD012
	88

85, 13-29	179-199	50-70
	·	
2: 1, 4: 1, 5: 0 2, 1, \$0222: 1, and	5: 4, 5: 3, 6: 3, 6: 6, 6, 1, L0805: 7: 2, 7: 2, 7: 1, 7: 1, 7	ლეგებე — ლეგებე —
AR033: 2, AR060: 2, AR089: 1, AR052: 1, AR055: 1, AR104: 1, AR061: 0, AR039: 0 H0693: 8, L0755: 2, L0731: 2, H0341: 1, S0222: ., L0769: 1, L0800: 1, L0665: 1, S0216: 1 and H0521: 1.	AR055: 6, AR033: 4, AR096: 3, AR052: 3, AR061: 3, AR089: 3, AR060: 3, AR053: 3, AR039: 2, AR104: 0 L0777: 7, L0750: 6, L0748: 5, L0779: 4, L0805: 2, L0517: 2, L0439: 2, L0740: 2, L0747: 2, L0759: 2, H0580: 1, S0010: 1, T0003: 1, H0622: 1, S0036: 11, L0764: 1, L0803: 1, H0144: 1, S3014: 1, L0749: 1 and L0758: 1.	LR089: 3, AR053: 3, LR052: 2, AR096: 2, LR104: 2, AR039: 2, LR055: 2, AR033: 2, LR060: 1, AR061: 1 H0651: 8, L0744: 7,
AR033: AR089: AR055: AR061: AR061: L0731: 2, L0769: 1, L0769: L0665: 1, H0521: 1.	<u> </u>	4444
	Pro-29 to Lys-34, Ser-91 to Thr-97.	1505 Val-4 to Thr-11, Ile-15 to Asn-20, Arg-35 to Lys-44.
	1504	1505
	51 - 860	85 - 480
	66	100
	661694	662513
	HAGBC45	HNTNT65
	68	06

VO 01/90304			-, <u>-</u>		PCT/US01/164
		,			
.0123: .0424:	0519:	0662:	0546:	0002:	7793: 10672: 7747:
L0748: 6, H0620: 4, S0360: 3, S0142: 3, L0755: 3, H0638: 2, H0052: 2, H0123: 2, H0083: 2, H0615: 2, H0639: 2, H0624: 3, H0615: 3, H0639: 2, H0424: 3, H0615: 3, H0639: 2, H0424: 3, H0615: 3, H0639: 3, H0624: 3, H0639: 3, H0624: 3, H0639:	2, 100153; 2, 100545; 2, H0059; 2, L0659; 2, L0519; 2, L0438; 2, S0378; 2, S3012; 2, S3014; 2, L0743; 2, L0750; 2, L0758; 2,	L0589: 2, H0656: 1, H0662: 1, S0420: 1, S0358: 1, S0408: 1, H0637: 1, S0222: 1, H0574: 1, S0280: 1,	LOC21: 1, H0544: 1, H0546: 1, H0545: 1, H0545: 1, H0081: 1, H0188: 1 H0687: 1, H0188: 1	H0292: 1, H0252: 1, H0673 1, S0036: 1, H0100: 1, H0641: 1, S0144: 1, S0002: 1, L0761: 1, L0643: 1,	1, L0375: 1, L0805: 1, L0776: 1, L0783: 1, L0793: 1, L0665: 1, S0053: 1, H0520: 1, H0658: 1, H0672: 1, H0522: 1, S0406: 1, H0436: 1, S0037: 1, L0747:
L0748: 6, H0620: 4, S0360: 3, S0142: 3, L0755: 3, H0638: 2, H0052: 2, H0123 2, H0083: 2, H0328: 2, H0615: 2, H0039: 2, H0424	10059: 2, 10059: 2, 1 10438: 2, 50378: 2, 1 1012: 2, 53014: 2, L 10750: 2, L0758: 2	L0589: 2, H0656: 1, E 1, S0420: 1, S0358: 1, S0408: 1, H0637: 1, S 1, H0574: 1, S0280: 1	0021: 1, H0544: 1, F H0545: 1, H0081: 1 0012: 1, H0266: 1, F H0687: 1 H0288: 1	10292: 1, H0252: 1, 1, S0036: 1, H0100: 1, H0100: 1, L0641: 1, S0144: 1, S01643: 1, L0761: 1, L0650: 1, L0	1, L0375: 1, L0805: 1, L0776: 1, L0783: 1, L, L0665: 1, S0053: 1, H0520: 1, H0658: 1, F1 H0658: 1, F1 H0636: 1, S0037: 1, L04036: 1, S0037: 1, L04036: 1,
3, S01 1, S01 1, S01 1, H063 1, H061	H005 H005 S3012 7, L07	1, S0408 20408 11, H00	1, H02 H001;	H029 1, S00 1, L07 1, L07	1, 1.0776 11, 1.06776 11, 1.0622 11, 1.0633
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			#46#		
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	8-35, 38- 56, 59-75	45-69, 76- 101, 115- 131	41-57
ļ	56,	45- 101 131 131	41
	6q22.1-22.3 120110, 121014, 142470, 156225, 164200, 164200, 601316, 601410, 601757	16p12-p13.1 108730, 147781, 172471, 172471, 186580, 266600, 278760, 600760, 600761, 600761, 600761,	
L0731: 1, S0031: 1, S0434: 1 and L0366: 1.	AR096: 6, AR052: 4, AR060: 4, AR055: 4, AR033: 4, AR039: 4, AR104: 3, AR089: 3, AR053: 3, AR061: 3 L0766: 4, L0748: 4, L0747: 4, L0752: 3, L0759: 3, S0212: 1, S0356: 1, H0188: 1, H0040: 1, L0772: 1, L0774: 1, S0328: 1, L0749: 1, L0755: 1, L0596: 1 and H0667: 1.	AR052: 5, AR089: 5, AR052: 5, AR089: 5, AR060: 4, AR096: 4, AR055: 3, AR104: 3, AR061: 3, AR039: 1 L0439: 4, L0418: 1, S0010: 1, L0455: 1, S0028: 1 and L0741: 1.	AR089: 28, AR039: 26, AR096: 25, AR052: 16,
	Asn-87 to Asn-92.	1507 Pro-27 to Ala-37.	1508 Glu-98 to Gln-106.
	1506	1507	1508
	825 - 1148	512	112 - 543
	101	102	103
	665234	666416	666429
	HTTAASO	HAGBX32	HHTMM1 8
	91	8	83

	T	
	84 84 84 84 84 84 84 84	123-139
	4	
	565: 34: 222: 44: 940: 94: 518:	
AR053: 14, AR060: 14, AR033: 12, AR104: 12, AR061: 3, AR055: 3 S0220: 1	AR052: 3, AR053: 3, AR033: 2, AR055: 2, AR104: 1, AR096: 1, AR061: 1, AR096: 1, AR089: 1, AR039: 0 S0422: 7, L0748: 6, L0664: 4, H0581: 3, L0665: 3, H0038: 2, H0659: 2, L0743: 2, L0751: 2, S0434: 2, L0596: 2, L0592: 2, L0411: 1, H0556: 1, H0222: 1, H0656: 1, S0116: 1, S0358: 1, S0132: 1, S0376: 1, H0977: 1, H0013: 1, S0142: 1, S0002: 1, H0622: 1, L0662: 1, L0794: 1, L0766: 1, L0791: 1, H0547: 1, H0519: 1, H0518: 1, H0521: 1, L0749: 1,	AR096: 1, AR060: 0, AR033: 0, AR061: 0,
AR053: 1 AR033: 1 AR061: S0220: 1	AR052: AR033: AR061: AR089: S0422: 7 L0664: 4, 3, H0038: L0711: 1, 1, S0360: S0476: 1, 1, R0622: 1, 1, R0642: 1, 1, L0766: H0647: 1, 1, L0766: H0647: 1, 1, L0766: L0777: 1	AR096: AR033:
	Ser-14 to Arg-20, Pro-92 to Ala-97, Glu-104 to His-110.	1510 Ala-62 to Glu-74.
	1509	1510
	. 528	26 - 469
	104	105
·	67779	668286
	HHFGR08	ннвеи19
	a	95

	59-75, 1- 17, 10 4 120, 169- 185	370-406, 10-38, 430-456, 262-279, 338-354, 303-320, 476-492, 105-121, 180-196	54-71
	·	·	
AR055: 0, AR089: 0, AR053: 0, AR104: 0, AR052: 0, AR039: 0 H0036: 1, L0471: 1, H0373: 1, L0804: 1 and H0665: 1.	AR096: 7, AR053: 5, AR039: 5, AR060: 3, AR052: 3, AR104: 3, AR089: 3, AR033: 2, AR061: 1, AR055: 0 H0580: 1, T0042: 1, S0002: 1 and L0439: 1.	AR033: 8, AR055: 7, AR060: 6, AR089: 4, AR052: 4, AR061: 3, AR096: 3, AR053: 2, AR104: 1, AR039: 1 H0561: 2, H0539: 2, S0276: 2, H0294: 1, S0212: 1, S0132: 1, H0431: 1, S0005: 1, H0544: 1, H0123: 1, H0266: 1, H0288: 1, H0039: 1, H0040: 1, H0547: 1, H0519: 1, S0044: 1, H0555: 1 and S0242: 1.	AR096: 4, AR089: 2, AR053: 2, AR052: 2,
	Tyr-35 to Gln-42, AR096: Asp-141 to Gly-160. AR039: AR089: AR061: H0580:	Arg-54 to Trp-62, Pro-68 to Ile-77, Asn-124 to Ala-130, Arg-155 to Lys-161, Ser-166 to Glu-178, Ile-407 to Ser-413, Pro-494 to Met-507, Pro-510 to Asp-516.	
	1511	1512	1513
	34 - 627	246 - 1880	10 - 618
	106	107	108
	985029	672653	082299
	HWBBB21	HAIDX85	HIMIMA VO 6
	96		86

WO 01/90304		FC1/USU1/10
,	79-104	59-75, 84- 100, 23-39
AR033: 2, AR055: 2, AR060: 2, AR061: 1, AR039: 1, AR104: 1 L0766: 3, H0413: 2, L0794: 2, H0659: 2, H0581: 1, S0314: 1, H0591: 1, T0042: 1, H0494: 1, L0769: 1, L0667: 1, L0800: 1, L0662: 1, L0666: 1, H0414: 1, H0658: 1, L0748: 1, L0755: 1, L0731: 1, L0758: 1, H0444: 1, S0242: 1 and H0542: 1.	AR033: 3, AR104: 2, AR096: 2, AR053: 2, AR039: 2, AR089: 1, AR052: 1, AR060: 1, AR061: 1, AR055: 0 L0769: 3, L0747: 3, L0759: 3, L0783: 2, L0438: 2, H0539: 2, L0439: 2, L0758: 2, L0589: 2, L0717: 1, L0598: 1, L0520: 1, L0794: 1, L0375: 1, H0144:	AR053: 52, AR052: 44, AR055: 40, AR104: 28, AR033: 28, AR089: 27, AR060: 23, AR061: 22,
∢∢∢∵∺∺∺∺∺∺	Ile-52 to Ser-59, AR033: Arg-106 to Asn-111, AR096: Gln-122 to Lys-130. AR039: AR052: AR061: L0769: 2, H0539 L0758: 2 L0758: 2 L0798: 1 and L0	Pro-13 to Arg-23. A A A A A A A A A A A A A A A A A A A
	1514	1515
	- 291 - 680	408 - 725
	109	110
	677920	678316
•	HISAM25	HRODX93
	66	100

											_																
	137-155,	I-19		,																							
													•								 -						
AR096: 22, AR039: 20 H0052: 1 and H0598: 1.	AR089: 3, AR033: 2,	AR053: 1, AR051: 1,	_	0	L0748: 11, L0749: 9,	S0408: 6, S0002: 4, L0776:		S0436: 4, L0588: 4, H0638:		L0646: 3, S0126: 3, L0758:				_	2, L0483: 2, T0042: 2,		7.7	L0803: 2, L0783: 2, L0665:	2, L0438: 2, H0659: 2,	S0152: 2, H0704: 2, L0779:	2, L0731: 2, L0759: 2,	S0434: 2, L0591: 2, L0599:	2, H0653: 2, H0685: 1,	H0583: 1, H0657: 1, H0656:	1, S0116: 1, S0001: 1,	H0483: 1, S0442: 1, S0376:	1, S0468: 1, H0619: 1,
	Asp-23 to Glu-28,	Ser 49 to Pro-54, Glu-61 to Thr-67.	Glu-72 to Asp-81,	Glu-83 to Asp-118,	Gly-156 to Arg-162,	Asp-184 to Tyr-205,	Met-251 to Asp-257,	Gln-273 to Asp-278,	Ser-284 to Tyr-293,	Phe-333 to Ser-338,	Lys-351 to Arg-357,	Gly-367 to Asp-375,	Asn-399 to Glu-414,	Gln-424 to Arg-443,	Glu-447 to Glu-457,	Arg-462 to Lys-476,	Lys-485 to Phe-492.										
	1516			• •			-									-						•					
	238 -	1713	•																								
	111		•																								
	678819						•		•								_		-								
	HLJDK82																			.,,		·	•				
	101																										

	T
	73-90, 12-
·	
H0393: 1, S0278: 1, H0549: 1, H0574: 1, H0075: 1, H0599: 1, H0036: 1, H0590: 1, S0010: 1, H0251: 1, T0115: 1, H0530: 1, H0572: 1, L0471: 1, H0014: 1, H0628: 1, L0055: 1, H0628: 1, H0708: 1, H0063: 1, H0648: 1, H0708: 1, H0663: 1, S0438: 1, S0440: 1, H0646: 1, L0769: 1, L0637: 1, L0644: 1, L0773: 1, L0662: 1, L0659: 1, L0526: 1, L0809: 1, L0730: 1, L0666: 1, L0659: 1, L0569: 1, L0666: 1, L0663: 1, S0374: 1, H0435: 1, H0670: 1, H0672: 1, H0631: 1, S0406: 1, H0671: 1, S0432: 1, L0769: 1, L0752: 1, S0031: 1, S0260: 1, L0581: 1, L0608: 1, L0762: 1, S00242: 1, H0672: 1, H0423: 1, H0672: 1, H0672	AR033: 5, AR089: 4,
	1517
	164-
	112
	682668
	HCFMJ37
	102

																		_
82	87-105, 31-47																	
							-						·		······			
						.		_	. <u>.</u>	<u></u>		:8:	·	ë		<u>-:</u>		5:
.096: 3, .053: 2, .061: 1,	15, AR039: 14, 12, AR052: 12,	11, AR060: 10, 9, AR061: 9, 8, AR096: 7	H0666: 13, H0620: 7, .0731: 7, L0747: 6, L0659:	(, L0740: 5, L0750: 5, L0757: 5, S0360: 4, H0123:	135: 4,	0666: 4, L0665: 4, S0028:	, L0748: 4, L0777: 4, 0588: 4, S0420: 3, S0358:	545: 3,	H0046: 3, H0284: 3, L0650:	s, LU3/2: 3, LU382: 3, H0352: 3, H0592: 2, H0544:	1266: 2,	H0286: 2, H0252: 2, H0428:)551: 2,	H0100: 2, S0210: 2, L0763:	774: 2,	0661: 2, L0518: 2, H0547:	037: 2,	<i>0</i> 751: 2, L <i>0</i> 752: 2, L <i>0</i> 755:
R060: 3, AR096. R052: 3, AR053: R055: 1, AR061: R104: 0 H0423: 1			H0666: 13, H0620: 7, 20731: 7, L0747: 6, I	5, L <i>074</i> 0: 5, L <i>075</i> 0: 5, L <i>0757</i> : 5, S0360: 4, H0	, S0022: 4, H0135: 4,	6: 4, L066	4, L0748: 4, L0777: 4, L0588: 4, S0420: 3, St	, H0208: 3, H0545: 3,	6: 3, H028	3, LU3/2: 3, LU3&2: 3, H0352: 3, H0592: 2, F	2, H0024: 2, H0266: 2,	6: 2, H02;	2, H0628: 2, H0551: 2	0: 2, S021	2, L0770: 2, L0774: 2,	1: 2, L051	2, H0670: 2, S0037: 2,	1: 2, L075
AR060: AR052: AR055: AR104: H0423:	AR055: AR089:	AR033: AR053: AR104:	H06 L073	5, 1.0	4, S0	<u>1</u> 066	4, 1 0, 8,01	3, H0	H004	3, LO H035	2, H0	H028	2, H0	H010	2,10	1066	2, H0	1075
		ı																
									,									
	1518																	
532	373 - 26																٠	
	113									 -								
	682949			,							· -							
	HMWAPI 7																	
	103					<u></u>												

	92-120,	30-50, 61-	77																									
					<u>,</u>							•			 .	_	···-		• • •			-						
67: 1.	AR055: 25, AR052: 25, AR053: 22, AR033: 18,	8, AR060: 15,	15, AR039: 15,	AR061: 14, AR104: 14	L0758: 7, L0766: 5,	.0558: 5, L0750: 5, S0360:	4, S0410: 4, L0747: 4,	S0007: 3, S0438: 3, L0763:	3, L0769: 3, L0775: 3,	S0380: 3, S0404: 3, L0748:	3, L0754: 3, L0749: 3,	L0759: 3, H0423: 3, H0661:	2, S0132: 2, H0441: 2,	H0494: 2, L0506: 2, L0761:	2, L0554: 2, L0523: 2,	.0776: 2, L0526: 2, L0532:	2, L0665: 2, S0126: 2,	S0378: 2, H0522: 2, L0742:	2, L0752: 2, L0731: 2,	J0757: 2, S0040: 1, H0717:	l, H0294: 1, S0134: 1,	H0657: 1, H0381: 1, H0341:	1, H0483: 1, H0669: 1,	H0638: 1, S0358: 1, S0444:	1, S0408: 1, H0208: 1,	H0351: 1, S0278: 1, H0392:	1, H0333: 1, L0622: 1,	H0486: 1, T0039: 1, L0021:
1 and H0667: 1		AR089:	AR096: 1	AR061: 1	L0758: 7	1.0558: 5,	4, S0410:	80007: 3,	3, 1.0769:	S0380: 3,	3, L0754:	1.0759: 3,	2, S0132:	H0494: 2,	2, L0554:	1.0776: 2,	2, L0665:	S0378: 2,	b, L0752:	L0757: 2,	1, H0294:	H0657: 1,	1, H0483:	H0638: 1,	1, SO408:	H0351: 1,	1, H0333:	H0486: 1,
	Ala-4 to Phe-9, Thr-155 to Asn-162.																										•	
	1519			·												_									."			
	34 - 519																					_						
	114																						•					
	684293												_	-								,						
	HMCFA76																											
	<u>5</u>																											

/U 01/90304 PC	1/0301/10450
	126-143, 292-308, 90-106, 252-268,
	106300, 108800, 120290, 120290,
	6p21.3
1, H0575: 1, S0010: 1, H0150: 1, H0086: 1, L0471: 1, H0688: 1, H0181: 1, H0617: 1, H0688: 1, S0366: 1, H0376: 1, H0163: 1, H0038: 1, H0616: 1, H0038: 1, H0616: 1, H0038: 1, H0629: 1, H0280: 1, H0629: 1, L0762: 1, L0639: 1, L0662: 1, L0767: 1, L0364: 1, L0574: 1, L0364: 1, L0577: 1, L0577: 1, L0540: 1, L0657: 1, L0517: 1, L0540: 1, L057: 1, L0663: 1, S0052: 1, H0689: 1, H0689: 1, H0660: 1, H0679: 1, S0028: 1, S0037: 1, H0644: 1, R0445: 1, H0559: 1, S0434: 1, H0667: 1, H0640: 1, H0667: 1,	1520 Pro-29 to Asn-35, AR055: 11, AR052: 10, Val-184 to Arg-191, AR033: 8, AR060: 7, Thr-219 to Thr-225, AR061: 7, AR089: 7, Ala-273 to Ser-281, AR053: 6, AR096: 5,
	115 145 - 15
	684309
,	105 HTHCM28
	ĭ

164-180	
120810, 120820, 142853, 142853, 150270, 177261, 177900, 201910, 235200, 235200, 235200, 235200, 236550, 600261, 600261, 602280,	
	•
Gly-319 to Glu-327, AR104: 5, AR039: 4 Gly-339 to Ser-345, L0748: 10, H0457: 5, Thr-358 to Gly-363, L0758: 4, L0776: 3, L0790: Lys 410 to Phe-416. 3, L0665: 3, H0617: 2, L0803: 2, L0644: 2, L0747: 2, L0588: 2, L0604: 2, H0265: 1, H0583: 1, S0116: 1, S0212: 1, S0442: 1, S0132: 1, H0351: 1, H0036: 1, H0441: 1, H0013: 1, S0010: 1, H0327: 1, H0046: 1, H0361: 1, S0366: 1, H0135: 1, H0590: 1, H0040: 1, H0529: 1, L0771: 1, H0059: 1, L0771: 1, L0771: 1, L0659: 1, L0771: 1, L0659: 1, L0771: 1, L0659: 1, L0771: 1, L0659: 1, L0789: 1, L0666: 1, L0663: 1, L0789: 1, L0669: 1, L0669: 1, L0789: 1, L0689: 1, L0789: 1, L07899: 1, L0789: 1, L07899: 1, L0789: 1, L07899:	H0435: 1, H0648: 1, H0651: 1, S0330: 1, S0380: 1, H0436: 1, L0751: 1, L0756: 1, L0731: 1, L0596: 1, L0589: 1, L0592: 1, S0011: 1, S0026: 1, S0276: 1 and

112410, 70-86 113520, 135700, 168470, 186940, 200990, 602096 602096 47-66, 275-291, 146-162, 99-115	
12p12	
H0423: 1. AR039: 6, AR096: 4, AR033: 4, AR052: 3, AR104: 3, AR052: 3, AR089: 3, AR060: 3, AR055: 2, AR061: 2 H0170: 1, H0484: 1, S0360: 1, H0309: 1, H0040: 1, L0611: 1, L0596: 1, H0542: 1 and H0543: 1. AR060: 5, AR052: 5, AR089: 4, AR053: 3, AR089: 4, AR053: 3, AR096: 3, AR055: 3, AR096: 3, AR055: 3, AR096: 2, AR104: 1 L0779: 4, S0360: 3, L0779: 4, S0360: 3, L0779: 4, L0637: 1, S0007: 1, S0016: 1, H0415: 1, H0486: 1, H0069: 1, H0427: 1, S0280: 1, H0543: 1, H0014: 1, S0214: 1, H0328: 1, H0614: 1, S0214: 1, H0543: 1	H0628: 1, S0440: 1, H0529: 1, L0766: 1, L0650: 1, L0675: 1, L0776: 1, L0655:
Thr-2 to Glu-13, Asn-19 to His-56, His-140 to Pro-148.	
1521	-
180 - 623 623	
117	
685054	
HHEDB45	
106	

T		101/0501/10
	89-106	301-338, 16-32
558:	803:	69: 74: 74:
1, L0783: 1, L0809: 1, S0374: 1, H0693: 1, H0658: 1, L0745: 1, L0752: 1, L0731: 1, L0757: 1, L0485: 1 and H0422: 1.	AR089: 2, AR039: 1, AR055: 1, AR096: 1, AR053: 1, AR104: 1, AR060: 0, AR061: 0, AR033: 0, AR052: 0 L0805: 2, L0749: 2, H0024: 1, H0112: 1, L0803: 1, H0660: 1, S0330: 1, L0748: 1, L0747: 1 and S0242: 1.	AR089: 8, AR055: 7, AR039: 6, AR033: 6, AR052: 6, AR060: 6, AR096: 5, AR104: 4 L0747: 14, L0439: 11, L0731: 8, L0438: 6, L0769: 5, L0766: 5, L0809: 5, L0749: 5, H0251: 4, H0124: 4, H0052: 3, H0545: 3, L0770: 3, L0804: 3, L0774: 3, L0776: 3, L0659: 3, L0663: 3, H0547: 3, L0748: 3, L0757: 3, L0758: 3,
		Pro-89 to Gly-96, Gly-119 to Leu-125, Thr-135 to Pro-141, Thr-160 to Arg-170, Glu-189 to Glu-196, Asp-229 to Asp-236, Arg-278 to His-286, Asn-337 to Tyr-348.
	1523	1524
	324 - 713	24 - 1067
	118	119
	685340	685495
	HFIZNSS	HCE1U38
	108	109

	103-123, 143-160	62-78, 105-121
	,	
.0658: 3014: 7780:	0, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,	
H0683: 1, H0659: 1, H0658: 1, H0670: 1, S0044: 1, H0187: 1, H0626: 1, S3014: 1, L0740: 1, L0751: 1, L0750: 1, L0786: 1, L0759: 1, S0260: 1, L0591: 1, L0593: 1 and H0543: 1.	AR089: 0, AR096: 0, AR1060: 0, AR1061: 0, AR1064: 0, AR055: 0, AR055: 0, AR052: 0, AR039: 0 L0517: 4, L0769: 3, L0776: 3, L0776: 3, L0790: 3, L0743: 2, L0754: 2, H0341: 1, S0132: 1, H0550: 1, H0036: 1, L0142: 1, H0671: 1, L0761: 1, L0764: 1, L0777: 1, L0755: 1, L0758: 1 and L0697: 1.	AR096: 4, AR055: 3 AR061: 3, AR060: 3 AR053: 3, AR052: 3
H0683: 1 1, H0670 H0187: 1 1, L0740; L0750: 1, 1, L0759; L0591: 1, H0543: 1	AR060: AR104: AR052: L0517: L0776: 3 2, L0754: 1, S0132: H0036: 1 1, L0761: L0805: 1 1, L0755: 1 1, L0761: L0805: 1 1, L0755: 1 1, L0755: 1 1, L0755: 1	AR096: AR061: AR053:
		1526 Glu-10 to Thr-15, Arg-33 to Glu-38, Leu-54 to Gly-59,
	1525	1526
	735	1521 - 1096
	120	121
	685604	686533
	HNFIL36 685604	HSKZB03
		111

		102-122
AR089: 2, AR033: 2, AR104: 2, AR039: 0 S0126: 8, S0420: 6, L0757: 6, S0212: 4, L0777: 4, H0662: 3, L0743: 3, L0608: 3, H0653: 3, H0667: 3, H0546: 2, L0764: 2, L0566: 2, H0660: 2, S0027: 2, L0769: 2, L0764: 2, L0759: 2, L0769: 1, H0665: 2, S0180: 1, H0665: 2, S0180: 1, H0665: 1, H0013: 1, L0021: 1, H0599: 1, H0036: 1, H0083: 1, L0669: 1, S0318: 1, S0316: 1, S0318: 1, S0316: 1, S0364: 1, H0413: 1, H0494: 1, S0150: 1, L0776: 1, L0776: 1, L0763: 1, L0776: 1, L0776: 1, L0763: 1, H06690: 1, H06689: 1, H06690: 1, H06689: 1, S0037: 1, S00	1, 2023; 1, 2021; 1, S0028: 1, L0780: 1, L0731: 1, H0668: 1, S0194: 1 and S0196: 1	AR039: 5, AR089: 3,
Gly-86 to Trp-101, Pro-123 to Thr-133.		Leu-27 to Ser-41.
		1527
		12 - 416
		122
		688935
		HNTMZ26
		112

7 0 01/20304	1 0 17 0 5 0 17 10 4 5 0
	36-70, 25- 41, 67-83
AR096: 3, AR052: 3, AR104: 2, AR060: 2, AR053: 1, AR061: 1, AR055: 1, AR033: 1 L0748: 5, H0519: 3, H0486: 2, H0179: 2, H0509: 2, H0521: 2, L0588: 2, L0595: 2, H0624: 1, H0650: 1, H0657: 1, H0656: 1, S0444: 1, H0580: 1, S0046: 1, H0188: 1, H0599: 1, S0474: 1, L0471: 1, H0266: 1, H0561: 1, H0633: 1, L0637: 1, H0144: 1, H0520: 1, H0547: 1, H0539: 1, S0378: 1, L0602: 1, S0146: 1, S3014: 1, L0756: 1, L0759: 1, L0480: 1, L0596: 1, L0608: 1, S0026: 1, H0542: 1, H0543: 1 and H0542: 1, H0543: 1 and	AR096: 88, AR052: 86, AR053: 68, AR089: 63, AR060: 53, AR104: 44, AR033: 37, AR039: 36, AR061: 15, AR055: 10 S0053: 3, L0752: 3, L0794: 2, S0052: 2, H0660:
	1528 Gly-6 to Gly-14.
	68 - 370 1528
	123 68
	689978
	HHENC76
	113

	33-61	300-328, 1-21, 180- 196
		×
2, S0152: 2, L0595: 2, H0543: 2, H0583: 1, H0346: 1, T0109: 1, L0767: 1, L0768: 1, H0521: 1, L0745: 1 and S0194: 1.	AR039: 31, AR033: 26, AR104: 25, AR053: 22, AR052: 19, AR055: 19, AR089: 14, AR060: 13, AR096: 11, AR061: 10 L0439: 3, L0438: 2, L0756: 2 and S0388: 1.	AR033: 29, AR104: 25, AR060: 22, AR096: 17, AR089: 16, AR052: 13, AR039: 11, AR055: 9, AR053: 8, AR061: 5 L0752: 30, L0754: 17, L0740: 16, H0521: 14, L0439: 14, L0766: 12, S0003: 11, S0214: 11, L0777: 10, S0002: 8, L0776: 8, L0748: 8, L0755: 8, S0360: 7, L0665: 7, L0770: 6, L0666: 6, L0747: 6, L0774: 5, L0751: 5, S0222: 4, H0575: 4, H0622: 4, L0662: 4, L0775:
	Ser-25 to Lys-32, Glu-63 to Gly-68.	Gln-153 to Ser-163, Ser-172 to Glu-178, Ala-204 to Asp-210, Ile-222 to Ala-236, Lys-284 to Ser-291, Met-342 to Arg-348.
	1529	1530
	427	1184
	124	125
	691490	695741
	HHSG130	HE8EQ09
	114	115

O 01/90304			PCT/US01/164
		· · · · · · · · · · · · · · · · · · ·	
		·	
	10586: 2, .0471: H0040:	., .0520: .0783: ., .00406:	50040: 50212: 50045:
750: 4, 1 10362: 4 10380: 3, 10710: 3 10731: 3, 8 594: 3, 8	278: 2, 1 H0581: 1 H0581: 1 110: 2, 1 S0022: 2	422: 2, 1 LO768: 2, 2 659: 2, 1 LO438: 2 672: 2, 2 LO780: 2, 5	H0624: 1 2265: 1, 3 20114: 1, 3 341: 1, 3 418: 1, 5 50476: 1
S0380: 4, L0750: 4, L0758: 4, S0436: 4, L0362: 4, H0638: 3, H0580: 3, L0598: 3, S0374: 3, H0710: 3, H0522: 3, H0555: 3, L0356: 3, L0759: 3, L0594: 3, S0134: 5, L0759: 3, L0759:	2, 503/6: 2, 50046: 2, H0393: 2, 50278: 2, H0586: 2, H0156: 2, H0581: 2, H0421: 2, T0110: 2, L0471: 2, S6028: 2, S0022: 2, H0690: 2, H0591: 2, H0040:	2, HUSS1: 2, HO412: 2, H0494: 2, S0422: 2, L0520: 2, L0764: 2, L0768: 2, L0655: 2, L0659: 2, L0783: 2, L0664: 2, L0438: 2, H0648: 2, H0672: 2, S0406: 2, S0028: 2, L0780: 2, L0588: 2, L0599: 2, H0667:	2, S0196: 2, H0624: 1, H0171: 1, H0265: 1, S0940: I, H0713: 1, S0114: 1, L0811: 1, H0341: 1, S0212: I, S0001: 1, H0661: 1, H0305: 1, S0418: 1, S0045: I, S0132: 1, S0476: 1,
203.4 103.00 100	2, H 2, H 3, W 4, H 9, W 4, H 9, W 6, H 9, W 6	1, 1, 2, 1, 2, 1, 2, 1, 2, 1, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2,	1, H 1, H 1, H 1, K 1, K 1, K 1, K 1, K
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	139-158, 110-126
1, H0438: 1, H0013: 1, S0010: 1, S0665: 1, S0474: 1, H0327: 1, H0046: 1, L0157: 1, S0051: 1, T0010: 1, H0266: 1, H0179: 1, H0615: 1, H0179: 1, H0674: 1, H0163: 1, H0031: 1, H0569: 1, H01359: 1, H0569: 1, H0560: 1, H0359: 1, H0569: 1, L0762: 1, L0762: 1, L0371: 1, L0796: 1, L0762: 1, L0371: 1, L0796: 1, L0761: 1, L0796: 1, L0773: 1, L0521: 1, L0796: 1, L0761: 1, L0796: 1, L0773: 1, L0521: 1, L0677: 1, L0521: 1, L0677: 1, L0568: 1, S0330: 1, S0152: 1, H0696: 1, S0404: 1, S0037: 1, L0746: 1, L0779: 1, S0037: 1, L0707: 1, S0434: 1, L0608: 1, S0436: 1 and H0506: 1, S0456: 1 and H0506: 1, S0456: 1 and H0506: 1, S0456: 1 and	AR033: 7, AR052: 6, AR104: 5, AR060: 5,
	Ala-8 to Ser-15, His-36 to Glu-44,
	1531
·	26 - 499
	126
	698634
٥,	HJKSC77
	116

VO 01.	/903	04	•				_									_			·]	PC'	T/U	JS0	1/10	545 —
																								·				
	<u></u>		.99		71:	_	<u>\$</u>		26:		:09	-	71:		:83:		6		38:		Ä		27.		36:			
% % 96: 4 4, 4,	61: 2	 %	: 6, LOZ	75: 4,	3, H01	22: 2,	: 2, 1.07	65: 2,	2, 107	58: 2,	: 1, S03	36: 1,	1, 1, 1, 1, 2,	73: 1,	: 1, H03	36: 1,	:: 1, S04	46: 1,	1,106	73: 1,	1, 1,08	56: 1,	: 1, HO	90: 1,	: 1, S01	6: 1,	1, L07,	31:1
4, AR089: 4, AR096:	3, AR0	8, 1077	10362	5, 1.07	10759	: 2, S02	,10372	2,106	10740:	2, 1.07	, S0418	: 1, H00	S0346:	: 1, H03	, S0334	: 1, 500	, H0202	1, H06	1.0763:	1,107	10649	1, LO6	, H0691	: 1, H06	, H0660	1, S040	L0754:	1.107
AR053: AR039:	AR055: 3, AR061:	S0358:	0779: 6, L0362: 6, L0766:	i, L0752: 5, L0775: 4,	0803: 3, L0759: 3, H0171:	2, H0657: 2, S0222: 2,	H0441: 2, L0372: 2, L0784:	2, L0809: 2, L0665: 2,	S0126: 2, L0740: 2, L0756:	2, L0755: 2, L0758: 2,	HO170: 1, S0418: 1, S0360:	, H0632: 1, H0036: 1,	S0010: 1, S0346: 1, L0471:	, H0014: 1, H0373: 1,	H0266: 1, S0334: 1, H0328:	l, H0316: 1, S0036: 1	H0412: 1, H0202: 1, S0440:	1, S0150: 1, H0646: 1	S0422: 1, L0763: 1, L0638:	1, L0764: 1, L0773:	.0662: 1, L0649: 1, L0804:	., L0774: 1, L0666: 1	H0144: 1, H0691: 1, H0547	1, H0519: 1, H0690: 1	H0683: 1, H0660: 1, S0136:	1, S0404: 1, S0406:	S0028: 1, L0754: 1, L0749:	1, 10750; 1, 10731; 1,
<u>در حن</u> من	<u>∢</u>			<u>5</u>	<u> </u>	-03	<u>;;</u>	-01	S	.01	<u> </u>	<u></u>	.so		<u> </u>	工	<u> </u>		S	_	브		<u>æ</u>	=1	<u> </u>		S	<u></u>
Arg-65 to Gln-70, Asp-133 to Glu-138.				-																								
Arg-65 Asp-13																												
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			•			<u>.</u>	<u>-</u>					_			_													

WO 01/90	1304 PC1/U	201/10
	80-96, 33-	12-34, 98- 114
	08 64	
L0757: 1, H0445: 1, H0343: 1, S0011: 1, S0026: 1 and H0543: 1		AR052: 2, AR053: 2, AR039: 1, AR055: 1,
	Met-1 to Lys-6, Glu-52 to Thr-58, His-72 to Ala-77.	
	1532	1533
	154 - 471	350 - 694
	127	128
	699216	702658
	HDABD32	118 HWACC64 702658
	117	118

VO 01/	/9030)4																					PC	T/U	IS0	1/16	45
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033:	104	4.5.1	527: 4	74:4,1)543: 4	8: 3, F	581:3	51: 3, I	3518: 3	4: 2, S	250: 2	2.2.1	766: 2	6: 2, I	221: 1	10: 17	3589: 1	38: 1, 1	474: 1	4: 1, I	3634:	87: 1, 1	450:1	4: 1, L	769: 1	0: 1, I	776: 1
: 1, AR033: : 1, AR061:	0, AR	15, H	5, H(, H013	: 4, H(, S021	3, HO	,1076	: 3, H(, S011	: 2, H(, H00	2, 10	, HO57	: 1, HC	, H014	1, H(, H06	: 1, S0	, S021	1, H(, H00	: 1, S0	, S034	:1,10	, L080	1. L0806: 1. L0776:
AR060: AR089:	AR096:	H0425: 10, H0445: 7, H0556: 6, S0134: 5, H0656:	, H0486: 5, H0657: 4,	H0271: 4, H0134: 4, H0436:	4, H0542: 4, H0543: 4,	H0422: 4, S0218: 3, H0125:	, S0278: 3, H0581: 3,	H0090: 3, L0761: 3, L0768:	, H0710: 3, H0518: 3,	H0265: 2, S0114: 2, S0360:	, H0580: 2, H0250: 2,	H0069: 2, H0004: 2, H0318:	2, S0142: 2, L0766: 2,	.0775: 2, H0576: 2, L0748:	", T0002: 1, H0221:	H0220: 1, H0140: 1, H0341:	, H0255: 1, H0589: 1	H0638: 1, H0608: 1, H0635:	, H0427: 1, S0474: 1	H0050: 1, S0214: 1, H0428:	, H0039: 1, H0634: 1,	H0063: 1, H0087: 1, H0272:	1, T0041: 1, S0450: 1	S0144: 1, S0344: 1, L0762:	, L0770: 1, L0769:	.0667: 1, L0800: 1, L0774:	10806
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	82-98
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L0655: 1, L0607: 1, L0661: 1, L0659: 1, L0809: 1, L0787: 1, L0664: 1, S0052: 1, S0053: 1, H0698: 1, H0701: 1, S0330: 1, S0378: 1, H0521: 1, H0214: 1, L0756: 1, L0779: 1, L0777: 1, L0755: 1 and H0136: 1.	AR055: 10, AR052: 9, AR053: 7, AR060: 6, AR061: 5, AR033: 5, AR096: 5, AR104: 5, AR089: 4, AR039: 3 L0766: 13, L0749: 8, L0776: 6, L0803: 5, L0770: 4, L0805: 4, H0100: 3, L0777: 3, L0789: 3, L0748: 3, L0745: 3, L0779: 3, L0777: 3, T0002: 2, H0090: 2, L0800: 2, L0809: 2, H0134: 2, L0756: 2, H0341: 1, H0192: 1, S0476: 1, H0549: 1, S0222: 1, H0587: 1, H0013: 1, H0265: 1, T0103: 1, H0266: 1, H0067: 1, H0266: 1, H0284: 1, T0042: 1, L0796: 1, L0761: 1, L0363: 1, L0768: 1,
	Glu-49 to Gln-55, Asn-115 to Gln-136, Glu-154 to Asn-169, Ser-183 to Asn-191.
	1145 1145 1145
	129
	703503
	HMWIW4 6
	1119

WO 01/90304	FC1/USU1/1045
	108-124
L0636: 1, H0703: 1, S0126: 1, H0682: 1, S0404: 1, S0028: 1, L0754: 1, L0747: 1, L0750: 1, L0755: 1, L0757: 1, L0759: 1, S0026: 1 and H0136: 1.	AR052: 23, AR055: 16, AR053: 14, AR096: 10, AR089: 9, AR096: 8, AR061: 7, AR033: 6, AR039: 4, AR104: 4 L0747: 5, L0749: 5, L0764: 3, L0804: 3, L0755: 3, S0360: 2, H0135: 2, H0529: 2, H0696: 2, H0134: 2, S0406: 2, L0777: 2, L0731: 2, L0778: 2, L0362: 2, H0265: 1, H0294: 1, S0116: 1, S0418: 1, S0420: 1, S0132: 1, H0586: 1, H0533: 1, H0677: 1, H0083: 1, H0594: 1, S0022: 1, H0551: 1, H0413: 1, H0494: 1, H0560: 1, S0448: 1, S0440: 1, H0649: 1,
-	1535
	242 - 646
	130
	705030
	HSDIJ72
	120

	80-99	42-59, 15-
1, L0382: 1, S0126: 1, L0759: 1, H0667:	3: 29, 3: 27, 5, 5, 1 1 2, S0028:	5, : 3, : 3, : 2, . H0580: : 2, . H0519: : 2, . S0116: : 1,
L0783: 1, L0383: 1, L0382: 1, L0789: 1, L0666: 1, L0663: 1, H0520: 1, S0126: 1, H0689: 1, S0390: 1, L0751: 1, L0752: 1, L0759: 1, S0031: 1, S0260: 1, S0434: 1, L0597: 1, H0667: 1 and S0424: 1.	AR061: 165, AR033: 29, AR089: 28, AR060: 27, AR052: 5, AR055: 5, AR053: 5, AR096: 5, AR104: 2, AR039: 1 S0222: 2, L0439: 2, S0028: 1 and L0731: 1.	AR096: 6, AR053: 5, AR052: 5, AR055: 5, AR033: 4, AR060: 3, AR061: 3, AR089: 3, AR104: 2, AR039: 2 L0766: 7, H0521: 3, L0779: 3, H0543: 3, H0580: 2, H0509: 2, L0662: 2, L0803: 2, L0805: 2, H0519: 2, H0539: 2, L0756: 2, L0759: 2, H0637: 1, H0574: 1, H0421: 1, S6028: 1, S0003: 1, S0214: 1,
	Met-1 to Leu-6, Ala-10 to Tyr-15, Arg-65 to Gln-70, Pro-107 to Glu-116.	AAAA HOHOHHH
	1536	1537
	46 - 408	214 - 519
	131	132
	706987	707266
	HSLGO34	нтоля
	121	122

VO 01/90304			PC1/US01/16
	45-62	77-95, 5- 21	51-68
			116806, 120120, 120120, 120120, 120436, 120436,
-×			3p21.3
H0688: 1, H0591: 1, H0264: 1, S0210: 1, H0529: 1, L0794: 1, L0804: 1, L0664: 1, S0374: 1, H0672: 1, L0754: 1, H0445: 1, L0604: 1 and S0194: 1.	AR053: 18, AR052: 17, AR055: 15, AR096: 14, AR089: 11, AR060: 9, AR061: 8, AR033: 8, AR104: 7, AR039: 5 H0457: 2, T0023: 1, H0144: 1, H0436: 1 and H0677: 1.	AR039: 47, AR033: 18, AR053: 16, AR104: 14, AR089: 14, AR096: 14, AR055: 11, AR052: 10, AR060: 10, AR061: 7 L0758: 4, L0731: 2, S0192: 2, H0038: 1 and L0638: 1.	AR096: 20, AR039: 17, AR089: 13, AR052: 11, AR053: 10, AR055: 9, AR060: 9, AR104: 8, AR033: 8, AR061: 4 L0803: 14, S0474: 13, L0748: 13, S0408: 11,
	Ser-21 to Gly-28, Gly-36 to Arg-41, Arg-66 to Tyr-74.	Arg-39 to Thr-46.	Ser-108 to Gln-125, Thr-156 to Glu-166.
	1538	1539	1540
	36 - 362	129 - 533	132 - 635
	133	134	135
	707398	707878	708053
	НР DЕР35	HFIA W95	HMEIU36
	123	124	125

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138320,	108406,	182280,	600163					-																				· · ·	
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L0754: 9, S0422: 7, S0360:	6, LU/94: 0, LU6U9: 0,	L0758: 6, H0265: 5, L0770:	5, L0805: 5, L0666: 5,	.0749: 5, L.0755: 5, L.0731:	5, S0414: 4, H0581: 4,	H0271: 4, L0771: 4, L0439:	4, L0591: 4, H0327: 3,	H0457: 3, H0266: 3, L0804:	3, L0776: 3, L0659: 3,	.0518: 3, L0665: 3, L0751:	3, S0434: 3, S0436: 3,	S0412: 3, H0656: 2, S0116:	2, S0212: 2, H0661: 2,	S0358: 2, S0132: 2, H0574:	2, H0156: 2, S0010: 2,	H0009: 2, H0123: 2, H0087:	2, H0551: 2, L0598: 2,	.0763: 2, L0761: 2, L0662:	766: 2, L0655: 2,	0636: 2, L0664: 2, S0374:	2, H0547: 2, H0660: 2,	S0378: 2, H0436: 2, L0750:	2, L0756: 2, L0596: 2,	.0603: 2, H0136: 2, H0624:	1, H0556: 1, S0040: 1,	H0295: 1, S0114: 1, S0356:	1, S0442: 1, S0376: 1,	S0444: 1, H0730: 1, H0208:	1, S0045: 1, S0476: 1,
1075 1075		SCOT	5, 10	1.074	5, 504	H027	4.	H045	3,10	10518	3, 804	S0412	2, 502	80358	2, H0	H000H	2, HO	10763	2,103	10636	2, HO	80378	2, 1.07	10603	1, HO	H029	1, SO4	S044	1, 500
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	174-190 174-190	70-87
		120220, 120240, 123580, 151385, 171860, 190685, 236100,
		21422.3
L0742: 1, L0744: 1, L0745: 1, L0747: 1, L0752: 1, L0757: 1, L0759: 1, L0605: 1, L0595: 1, S0192: 1, H0542: 1, H0423: 1, H0422: 1, S0042:	AR053: 3, AR096: 3, AR039: 2, AR052: 2, AR104: 2, AR033: 2, AR089: 2, AR060: 1, AR055: 1, AR061: 1 L0779: 5, L0157: 2, L0803: 2, L0754: 2, L0595: 2, H0305: 1, H0589: 1, H0638: 1, H0351: 1, H0486: 1, L0021: 1, H0318: 1, H0596: 1, S0150: 1, S0144: 1, L0364: 1, L0766: 1, L0809: 1, L0532: 1, H0667: 1 and H0542: 1.	AR033: 13, AR089: 12, AR060: 8, AR053: 8, AR039: 7, AR055: 6, AR052: 6, AR096: 5, AR061: 4, AR104: 3 H0038: 4, H0529: 3, L0803: 3, L0747: 3, L0779:
	1541 Ser-76 to Ser-82.	1542 Ala-16 to Glu-36, Arg-51 to Thr-56, Glu-104 to Thr-112.
	30 - 668	95 - 748
	136	137
	708177	709347
	126 HHEDM89 708177	HKABW60 709347
	126	127

	24.45, <i>97-</i> 116, <i>67-</i> 84
236200, 240300, 267750, 600065, 601072, 601145	
3, H0341: 2, L0761: 2, L0794: 2, L0766: 2, L0805: 2, L0664: 2, L0777: 2, L0591: 2, L0485: 2, H0556: 1, H0583: 1, H0661: 1, H0662: 1, S0420: 1, S0410: 1, H0333: 1, H0574: 1, S0280: 1, H0318: 1, H0014: 1, H0687: 1, S0003: 1, H0615: 1, L0055: 1, H0598: 1, L0770: 1, L0769: 1, L0646: 1, L0770: 1, L0649: 1, L0646: 1, L0768: 1, L0649: 1, L0381: 1, L0806: 1, L0527: 1, L0659: 1, L0809: 1, L0787: 1, L0438: 1, L0322: 1, S0390: 1, L0757: 1, H0445: 1, L0592: 1 and	AR096: 5, AR053: 3, AR061: 3, AR052: 3, AR033: 3, AR089: 3, AR039: 3, AR104: 2, AR055: 2, AR060: 2 L0751: 6, H0510: 3, L0659: 3, L0439: 3, H0265:
	1543
	79 - 627
	138
	710542
	HWLFB40

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	56-74, 38- 54, 89-105
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2, S0212: 2, S0418: 2, H0509: 2, L0773: 2, L0438: 2, L0773: 2, L0438: 1, L0731: 2, L0754: 2, L0731: 2, L0581: 2, H0556: 1, H0650: 1, L0605: 1, S6022: 1, S6014: 1, H0581: 1, H0050: 1, L0471: 1, H0178: 1, H0050: 1, L0471: 1, H0135: 1, H0673: 1, H0135: 1, H0551: 1, S0372: 1, S0210: 1, L0770: 1, L0771: 1, L0768: 1, L0772: 1, L0770: 1, L0776: 1, L0770: 1, L0770: 1, L0776: 1, L0770: 1, L0770: 1, L0776: 1, L0772: 1, L0770: 1, L0776: 1, L0772: 1, L0777: 1, L0776: 1, L0770: 1, L0777: 1, L0776: 1, L0770: 1, L0777: 1, L07	AR053: 16, AR096: 11, AR053: 10, AR033: 9, AR052: 7, AR104: 7, AR089: 7, AR055: 6, AR060: 6, AR061: 3 L0438: 3, S0114: 1, H0580: 1, H0486: 1, H0706: 1, L0455: 1, H0561: 1, H0529: 1, H0658: 1 and L0439: 1.
·	Lys-18 to Ser-24.
	54-410 1544
	139 54
·	710974
	HDTDW40
	129

	1 0 1 / 0 5 0 1 / 1 0
122-138, 90-106, 145-161 85-117	93-110
·	
AR039: 46, AR052: 45, AR053: 36, AR096: 34, AR033: 27, AR055: 24, AR104: 24, AR089: 23, AR060: 18, AR061: 11 L0439: 3, L0438: 2, S0028: 2, H0656: 1, H0645: 1, H0369: 1, S0222: 1, S0346: 1, H0169: 1, H0591: 1, H0646: 1, H0520: 1, H0539: 1, L0746: 1 and L0366: 1. AR096: 3, AR052: 2, AR039: 2, AR055: 2, AR039: 2, AR061: 1, AR053: 1, AR104: 1	H0553: 2, L0754: 2, L0749: 1 and L0780: 1. AR089: 8, AR033: 8, AR060: 6, AR096: 2, AR061: 2, AR053: 1, AR052: 1, AR039: 0, AR104: 0 S0388: 1, H0083: 1 and L0777: 1. AR052: 17, AR053: 12,
AR039: AR053: AR104: AR060: 1, H0369: 1, H0544 H0591: 1 1, H0539 L0366: 1 AR039: AR039: AR039: AR039: AR039: AR039:	H0553: 2, L075- 1 and L0780: 1. AR089: 8, AR(AR060: 6, AR(AR051: 2, AR(AR052: 1, AR(AR104: 0 S0388: 1, H008 L0777: 1. AR052: 17, AR
	1547 Pro-8 to Thr-16, Glu-50 to Glu-60, Gln-67 to Arg-72, Lys-81 to Asn-94.
1545	1547
7 - 825 275 - 706	40 - 369
140	142
711111	712570
130 HEAAK34 711111	HHSF189
	132

AR053: 11, AR089: 8, AR060: 8, AR096: 7, AR061: 7, AR055: 4, AR104: 1, AR039: 0 L0740: 5, L0731: 5, L0740: 3, H0657: 2, L0779: 3, H0657: 2, L0779: 3, H0657: 2, L0779: 2, L0771: 2, L0753: 2, L0601: 2, H0265: 1, S014: 1, H0656: 1, H0580: 1, H0486: 1, S0010: 1, H065: 1, L0748: 1, L0768: 1, L0660: 1, L0663: 1, H0486: 1, L0660: 1, L056: 1, L0660: 1, L0596: 1, L0660: 1, L0596: 1, L0758: 1, L0596: 1, H0668: 1, L0748: 1, L0750: 1, L0758: 1, L0596: 1, H0668: 1, H0542: 1, AR052: 5, AR096: 5, AR052: 5, AR096: 5,		
8, 7, 4, 0 0 1,0766: 2, 1,0777: 2, H0656: 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,		
8, 4, 4, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,		
11, AR089: 8, 8, AR096: 7, 7, AR055: 4, 1, AR039: 0 5, L0731: 5, H0556: 3, L0766: 3, H0556: 3, L0777: 2, L0601: 2, L0776: 2, L0601: 2, S0114: 1, H0656: 1, H0488: 1, H0488: 1, H0691: 1, H0438: 1, H0591: 1, L056: 5, AR096: 5,	· · · · · · · · · · · · · · · · · · ·	
AR060: AR060: AR060: AR104: L0740: 4 1,0439: 4, 3, L0779: 4 1, H0580: 1, 1, L0648: 1, 1, L0650: 1, 1, L0666: 1, 1, L0666: 1, 1, L0668: 1, 1, L0788:	3, AR055: 2,	AR104: 2, AR060: 2,
Glu-31 to Arg-36, His-85 to Gly-92.		
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540	333	
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HMJAXI7		
134 HIM		

	171-188	48-64	111-127
·			
AR039: 2, AR061: 2 L0439: 4, L0777: 3, H0658: 2, S0114: 1, S0360: 1, L0717: 1, H0391: 1, H0486: 1, L0157: 1, H0172: 1, H0083: 1, H0551: 1, H0517: 1, L0769: 1, L0521: 1, L0768: 1, L0805: 1, L0664: 1, H0521: 1 and H0555: 1.	AR096: 2, AR060: 1, AR053: 1, AR033: 1, AR089: 0, AR061: 0, AR055: 0, AR104: 0, AR052: 0	AR039: 76, AR052: 40, AR033: 39, AR096: 39, AR055: 38, AR104: 33, AR050: 24, AR061: 20 L0485: 2, S0282: 1, S0418: 1, H0002: 1, H0253: 1, H0196: 1, L0794: 1 and L0787: 1.	AR096: 1, AR052: 1, AR089: 1, AR060: 0, AR061: 0, AR033: 0, AR039: 0, AR053: 0
		lle-95 to Ala-101, Leu-110 to Ser-128.	Glu-22 to Ala-29, Ser-47 to Arg-58, Ser-108 to Tyr-113.
·	1550	1551	1552
	271 - 849	40 - 480	281 - 661
	145	146	147
	717449	718574	718768
	HLJDZ45	136 HAHBC57	HLYDR60
	135	136	137

WO 01/90304 PCT/US01/16450

	94-110	76-99
S0182: 3, S0222: 2, H0445: 2, H0341: 1, H0151: 1, H0550: 1, T0039: 1, H0156: 1, H0275: 1, S0318: 1, S0316: 1, T0006: 1, H0040: 1, L0475: 1, S0344: 1, L0768: 1, L0766: 1, H0435: 1, L0750: 1, L0757: 1 and S0260: 1.	AR033: 4, AR039: 3, AR096: 2, AR089: 2, AR061: 2, AR052: 1, AR060: 1, AR104: 1, AR053: 0, AR055: 0 H0484: 1, S0280: 1, H0373: 1 and H0593: 1.	AR033: 4, AR089: 4, AR061: 2, AR060: 1, AR052: 1, AR104: 1, AR039: 0, AR055: 0, AR096: 0, AR053: 0 L0805: 3, L0439: 3, H0674: 2, L0518: 2, L0809: 2, L0789: 2, L0751: 2, L0758: 2, H0390: 1, H0544: 1, H0570: 1, S0051: 1, T0006: 1, L0769: 1, L0800: 1, L0794: 1, L0803: 1, L0661: 1, L0636: 1, L0529:
,		Arg-11 to Gly-16, Pro-35 to Phe-44.
	1553	1554
	10 - 372	105 - 431
	148	149
	719977	720237
	HCHMQ09 719977	HADMD75 720237
	138	139

WO 01/90304	PC1/US01/16450
	89-107
1, L0543: 1, L0665: 1, H0696: 1, H0694: 1, S0406: 1, L0747: 1, L0779: 1, L0777: 1, L0731: 1 and H0352: 1.	AR052: 3, AR096: 3, AR033: 2, AR053: 1, AR039: 1, AR104: 1, AR055: 1, AR089: 1, AR060: 1, AR061: 1 L0794: 10, L0803: 4, S0045: 3, H0486: 3, H0013: 3, H0251: 3, H0591: 3, H0265: 2, S0360: 2, S0222: 2, L0758: 2, L0591: 2, L0809: 2, H0519: 2, H0170: 1, H0556: 1, S0040: 1, S0114: 1, L0760: 1, H0492: 1, H0675: 1, H0178: 1, H0587: 1, H0620: 1, H0492: 1, H0641: 1, L0638: 1, L0761: 1, L0435: 1, L0774: 1, L0653: 1, L0663: 1, H0144: 1, L0438: 1, H0589: 1, H0659: 1, H0589: 1, H0659: 1,
	1555 Ala-7 to Lys-28, Gly-45 to Lys-55.
	1555
	51 - 473
	150
	720269
	HKADW4
	140

WO 01/903	04 FC1/0	USU1/1645(
	62-78	
1, L0754: 1, L0747: 1, L0750: 1, L0752: 1, S0434: 1, L0595: 1 and L0366: 1.	AR055: 16, AR039: 15, AR033: 15, AR053: 13, AR052: 10, AR104: 9, AR096: 10, AR104: 9, AR096: 10, AR104: 7 L0769: 4, S0126: 4, L0758: 4, L0755: 3, S0378: 2, L0748: 2, L0779: 2, L0592: 2, H0716: 1, H0656: 1, H0341: 1, S0418: 1, S0420: 1, H0675: 1, S0408: 1, H0580: 1, S046: 1, S0300: 1, H0673: 1, H0013: 1, S0344: 1, L076: 1, L076: 1, L076: 1, L0771: 1, L076: 1, L0774: 1, L0775: 1, L0375: 1, L0655: 1, L0382: 1, H0144: 1, H0690: 1, S0328: 1, H0710:	1, H0521: 1, L0731: 1, H0445: 1, H0667: 1, S0276: 1, H0543: 1, H0422: 1 and
	Gln-88 to Leu-99,	
	1556	
	28 - 327	
	151	
	721084	
	HFAUL30	
	141	

	70-87	71-87
		• .
S0446: 1.	AR104: 10, AR033: 7, AR052: 6, AR089: 4, AR053: 4, AR096: 3, AR039: 3, AR060: 3, AR055: 2, AR061: 0 L0766: 4, H0494: 2, L0755: 2, S0040: 1, S0420: 1, S0046: 1, S0132: 1, S0222: 1, H0438: 1, H0250: 1, S0010: 1, H0038: 1, H0538: 1, L0800: 1, L0773: 1, H0670: 1 and L0777: 1.	AR053: 42, AR096: 31, AR052: 30, AR089: 24, AR033: 23, AR104: 18, AR039: 18, AR055: 16, AR060: 16, AR061: 8 L0439: 9, H0013: 3, H0090: 2, H0561: 2, L0754: 2, L0731: 2, H0170: 1, H0341: 1, H0580: 1, H0485: 1, L0471: 1, H0024: 1, H0644: 1, H0591: 1, H0551: 1, L0766: 1, L0606: 1, L0659: 1, L0438: 1, L0352: 1, H0672: 1, H0521: 1, H0436: 1, H0527: 1, L0748:
	·	Leu-14 to Glu-23, Lys-41 to Arg-50, Pro-90 to Gln-96.
	1557	1558
	- 181 - 609	42 - 401
	152	153
	721126	721141
	HKADD23	HE8MO09
	142	143

WU 01/90304	101/0	201/10
106-127, 56-77, 80- 98	42-58, 73- 89, 120- 136	77-97, 14- 31
·	5 4 8 5 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8	
AR039: 20, AR089: 18, AR052: 18, AR053: 17, AR096: 17, AR033: 15, AR055: 15, AR104: 14, AR060: 13, AR061: 6 H0013: 1, L0761: 1 and	AR089: 6, AR033: 5, AR060: 5, AR053: 3, AR056: 3, AR061: 2, AR055: 2, AR104: 1 H0617: 9, H0549: 4, S0406: 4, L0439: 3, H0717: 2, H0255: 2, S0358: 2, H0550: 2, S0049: 2, H0494: 2, L0777: 2, H0713: 1, H0716: 1, H0421: 1, H0457: 1, S0132: 1, H0619: 1, L0021: 1, H0421: 1, H0457: 1, S0366: 1, H0529: 1, S0344: 1, L0657: 1, L0783: 1, L0761: 1, L0657: 1, L0783: 1, L0789: 1, H0593: 1, H0539: 1, H0593: 1,	AR055: 11, AR060: 7, AR096: 5, AR033: 5,
		AR
1559 Met-1 to Gly-7.	1560 Met-1 to Cys-18.	1561
593	600	34 - 591 1
154	155	156
721418	722648	722943
HE8FL67 721418	HEOOA49 722648	146 HMSJH49
144	145	146

	1-25, 86- 119, 142- 159, 79-95	89-107, 6- 22	41-58
	102540, 1 103581, 1 118511, 1: 146150, 227220, 243500, 254770, 601623, 601889, 601889, 602117		4
	15q13-q14 10 10 10 10 10 10 10 10 10 10 10 10 10		
AR052: 5, AR061: 5, AR039: 4, AR089: 3, AR053: 3, AR104: 3 L0539: 2, H0546: 1, S0386: 1, H0560: 1, S0002: 1, L0741: 1 and L0746: 1.	8, 8, 7, 5, 5 1.0758:	AR096: 3, AR039: 1, AR052: 1, AR089: 1, AR060: 1, AR055: 0, AR061: 0, AR033: 0, AR053: 0, AR104: 0 H0341: 1 and H0486: 1.	AR061: 1, AR033: 1, AR039: 0, AR089: 0, AR053: 0, AR096: 0, AR055: 0, AR060: 0, AR052: 0, AR104: 0
	Pro-28 to Ser-33, Pro-66 to Arg-79, Ser-163 to Gly-180.		Met-1 to Ala-7, His-24 to Pro-35.
	1562	1563	1564
	218 - 910	48 - 395	318 - 662
		158	159
	723491	724196	724352
	HARAX45	HDTES50	нк GBС30
	147	148	149

WO	01/90304		PCT/US01/164
	90-106, 42-58	43-59	221-238, 54-70
		126650, 126650, 154276, 173360, 173360, 602136, 602136, 602136,	116806, 120120, 120120, 120120, 120436, 120436, 138320, 168468, 182280, 600163
		75.pr	3p21.3
	AR052: 19, AR055: 18, AR089: 17, AR053: 14, AR033: 11, AR061: 9, AR060: 9, AR096: 8, AR039: 0, AR104: 0 L0766: 4, H0441: 1, L0744: 1 and L0596: 1.	AR039: 53, AR055: 28, AR053: 27, AR033: 23, AR052: 21, AR096: 21, AR104: 21, AR089: 18, AR060: 15, AR061: 13 H0618: 8 and H0253: 4.	AR104: 4, AR033: 4, AR089: 3, AR053: 3, AR052: 3, AR096: 2, AR061: 2, AR060: 2, AR055: 2, AR039: 2 L0803: 6, L0771: 5, L0439: 5, L0769: 4, L0805: 4, L0759: 4, L0747: 3, L0777: 3, L0758: 3, H0156: 2, H0618: 2, H0052: 2, H0545: 2, L0163: 2, H0644: 2, S0440: 2, L0644: 2,
	Glu-10 to Asn-15, Val-73 to Arg-83, Gly-118 to Ser-128.	1566 Met-1 to Ser-7.	Glu-122 to Lys-127, Glu-161 to Val-168, Thr-178 to Trp-189.
	1565	1566	1567
	90 - 500	218 - 577	127 - 888
	160	161	162
	724432	724950	725228
	HKIXO37	нт. нз9	HEQB181
	150		152

WO 01/90304 FC 1/05	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,
	22-63, 51- 67
L0766: 2, L0653: 2, L0665: 2, H0639: 2, L0748: 2, L0731: 2, L0593: 2, H0624: 1, H0556: 1, T0002: 1, H0713: 1, H0650: 1, H0657: 1, H0402: 1, S0132: 1, H0642: 1, H0486: 1, H0642: 1, H06486: 1, H0642: 1, H06486: 1, H0642: 1, H06486: 1, H0648: 1, H0674: 1, S0066: 1, H0674: 1, S0066: 1, H0674: 1, S0066: 1, H0674: 1, H0647: 1, S0144: 1, H0529: 1, L0763: 1, L0763: 1, L0772: 1, L0776: 1, L0869: 1, L0763: 1, L0763: 1, H0647: 1, S0126: 1, H0647: 1, L0763: 1, L0763: 1, L0763: 1, L0763: 1, L0763: 1, L0753: 1, L0750: 1, L0755: 1, L0750: 1, L0750: 1, L0750: 1, H0647: 1, L0750: 1, L0750: 1, H0647: 1, L0750: 1, L0750: 1, L0750: 1, L0750: 1, H0647: 1, L0750: 1, L0750: 1, L0750: 1, L0750: 1, L0750: 1, H0647: 1, H06	AR033: 28, AR060: 19, AR104: 19, AR089: 18,
	1568 Met-1 to Lys-11, Gln-72 to Gly-77.
·	1568
	215 - 568
	163
,	725655
	HAGES18
	153

WO 01/90304	, 					_	_							_						rc 	1/0	20.	1/10
	69-85, 27- 44, 112-	128				,				-													
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		-			-																		
AR096: 13, AR061: 8, AR055: 6, AR053: 5, AR052: 5, AR039: 3	AR104: 21, AR033: 17, AR055: 11, AR060: 6,	AR061: 6, AR039: 6,	AR089: 6, AR053: 5, AR052: 4, AR096: 4	L0439: 13, H0052: 8,	L0769: 5, L0755: 5, L0770:	4, L0754: 4, L0753: 4,	L0758: 4, L0794: 3, L0775:	3, L0806: 3, L0776: 3,	L0752: 3, S0360: 2, H0261:	2, S0388: 2, H0213: 2,	L0804: 2, L0774: 2, L0807:	2, L0779: 2, L0603: 2,	S0256: 1, H0255: 1, H0455:	1, H0009: 1, H0172: 1,	S0051: 1, T0010: 1, T0006:	1, H0033: 1, H0424: 1,	S0364: 1, S0036: 1, H0038:	1, H0131: 1, L0764: 1,	L0803: 1, L0805: 1, L0809:	1, L0787: 1, L0790: 1,	L0663: 1, H0521: 1, L0742:	1, L0751: 1, L0745: 1,	L0731: 1 and L0485: 1.
·	Arg-14 to Pro-20.																						
	1569																						
	183 - 575																						
	164																						
	725822									•													
	HHSGV20																						
	154							_															

PC 1/USU1/16450
34-54, 83- 101
136533, 180200, 180200, 180200, 180200,
13q14.1- q14.2
AR052: 4, AR039: 3, AR104: 3, AR033: 2, AR096: 2, AR060: 2, AR053: 2, AR055: 2, AR089: 1, AR061: 1
Arg-7 to Leu-15.
1571
71 - 403
166
728064
HRAA053
156

VO 01	/903	304		-						· <u>·</u>				•			_]	PC	Т/Т	JS0	1/1	645
600631																												
L0747: 21, L0740: 20, H0144: 17, L0663: 15,	L0666: 14, L0748: 14,	L0662: 12, L0665: 11,	H0656: 10, H0013: 10,	L0659: 10, H0672: 10,	L0758: 10, H0486: 9,	S0422: 9, L0766: 9, H0539:	9, L0731: 9, L0599: 9,	S0360: 8, S0222: 8, H0457:	8, H0090: 8, H0423: 8,	H0050: 7, L0471: 7, H0519:	7, H0648: 7, H0657: 6,	S0358: 6, H0024: 6, S0003:	6, L0598: 6, L0775: 6,	L0776: 6, L0744: 6, L0756:	6, L0777: 6, S0434: 6,	S0026: 6, S0116: 5, S0356:	5, S0444: 5, H0014: 5,	L0637: 5, L0646: 5, L0655:	5, L0809: 5, H0696: 5,	S0436: 5, L0608: 5, L0362:	5, S0412: 5, S0134: 4,	H0583: 4, H0650: 4, S0408:	4, S0045: 4, L0717: 4,	H0046: 4, H0622: 4, H0031:	4, H0163: 4, H0591: 4,	H0040: 4, T0067: 4, T0041:	4, L0764: 4, L0768: 4,	L0774: 4, L0375: 4, L0653:
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4, H0555:	L0591: 4,	S0442:	J, H0036:	3,	H0644:	3,	L0771:	3,	S0406:	3,	S0192:	2,	H0580:	2,	T0060:	2,	1.0163:	~	H0328:	2,	1.0455:	ر	H0641:	~	1000
10670: 4, 1.0750:	, H0422:	10341: 3,	, 3000/ 10586: 3,	, H0052	10553: 3,	, H0551:	10646: 3,	10664:	10660: 3,	L0746:	10445: 3,	, H0170:	10662: 2,	, \$0278:	0414: 2,	, H0599:	0178: 2,	, S0388:	10252: 2,	, H0688:	0674: 2,	, H0135:	0440: 2,	1.0520:	0.1000
4, S0374: 4, L0438: 4, H0520: 4, H0670: 4, H0555: 4, L0754: 4, L0750: 4,	L0755: 4, L0757: 4, L0591: 4, L0361: 4, H0422: 4,	H0624: 3, H0341: 3, S0442:	3, 303/0. 3, 3000/. 3, H0441: 3, H0586: 3, H0036:	3, H0581: 3, H0052: 3,	H0266: 3, H0553: 3, H0644:	, H0038: 3, H0551: 3,	H0647: 3, H0646: 3, L0771:	3, L0517: 3, L0664: 3,	H0593: 3, H0660: 3, S0406:	3, L0745: 3, L0746: 3,	.0752: 3, H0445: 3, S0192:	, H0542: 3, H0170: 2,	H0716: 2, H0662: 2, H0580:	2, H0619: 2, S0278: 2,	H0369: 2, S0414: 2, T0060:	2, H0156: 2, H0599: 2,	S0049: 2, H0178: 2, L0163:	2, H0051: 2, S0388: 2,	H0083: 2, H0252: 2, H0328:	2, H0615: 2, H0688: 2	F0023: 2, H0674: 2, L0455:	2, H0068: 2, H0135: 2,	H0100: 2, S0440: 2, H0641:	S0002: 2, L0520: 2,	OCAS O TOMOS O TOCES
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547:	605:	171:	,	940	0459:		132:		0461:		3331:		635:	_	318:		572:	•	1051:		:197		104
5: 2, HC 658: 2, 8: 2, S0	751: 2, 1: 2, 1.0	543: 2, I: 1, H0	265: 1,	6: 1, SC 713: 1.	1: 1, Hi	420: 1,	5: 1, S0	026: 1,	0: 1, H(600: 1,	3: 1, H(485: 1,	9: 1, HC	590: 1,	i: 1, HO	194: 1,	3: 1, HO	012: 1,	3: 1, S0	239: 1,	3: 1, HO	188: 1,	9.1.10
1. 2. LO 1. 2. LO 1. 2. HO 1. 4. HO	2, LO	2, HO	: 1, HO	i, H068 : 1. H0	H066	3: 1, 50	. S004	: 1, S6	, H055): 1, HO	, H033	: 1, HO	, H006	: 1, HO	, S0346	: 1, HO	, 1.0738	: 1, HO	, H037	: 1, HO	, S6028	: 1, HO	H003
2, L0555: 2, L0526: 2, L0518: 2, L0545: 2, H0547: 2, H0684: 2, H0658: 2, S0328: 2, H0478: 2, S0028:	, L0439; 2, L0751; 2, .0779: 2, S0031: 2, L0605:	2, L0590: 2, H0543: 2, S0452: 2, L0411: 1, H0171:	, L0615: 1, H0265: 1		10255: 1, H0661: 1, H0459:	, H0638: 1, S0420: 1	H0329: 1, S0046: 1, S0132:	l, H0393: 1, S6026: 1,	H0549: 1, H0550: 1, H0461:	, H0370: 1, H0600: 1,	H0587: 1, H0333: 1, H0331:	l, H0574: 1, H0485: 1,	0586: 1, H0069: 1, H0635:	1, T0082: 1, H0590: 1	S0010: 1, S0346: 1, H0318:	, H0374: 1, H0194: 1,	F0110: 1, L0738: 1, H0572:	, H0123: 1, H0012: 1,	H0015: 1, H0373: 1, S0051:	1, H0356: 1, H0239: 1,	H0594: 1, S6028: 1, H0267:	1, H0271: 1, H0188: 1	H0428: 1, H0039: 1, 1,0194:
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	PC1/USU1/10450
40-72	
456: ; 1. 731: 003:	580: 3344: 5602: 581: 7794:
1, H0667: 1, S0276: 1, S0424: 1, S0462: 1, S0456: 1, H0008: 1 and H0352: 1. AR096: 1, AR104: 1, AR089: 1, AR060: 1, AR061: 0, AR033: 0, AR039: 0, AR052: 0, AR055: 0, AR055: 0, AR055: 0, AR053: 0, L0740: 10, H0521: 8, L0659: 7, L0666: 7, L0731: 7, L0664: 6, L0754: 6, L0770: 4, L0771: 4, L0438: 4, H0547: 4, S0380: 1, A438: 4, H0547:	LU458: 4, HU547: 4, 50380: 4, S0152: 4, H0522: 4, L0755: 4, H0171: 3, S0212: 3, S0358: 3, H0623: 3, S0344: 3, H0546: 3, H0546: 3, H0548: 3, L0759: 3, L0769: 3, S0126: 3, S0192: 3, S0242: 3, S0192: 3, S0242: 3, S0192: 3, S0242: 3, L0599: 2, H0560: 2, H0560: 2, L0483: 2, H0169: 2, H0560: 2, L0775: 2, L0766: 2, L0775: 2, H0660: 2, L0777: 2, H0660:
1, F 804 1, B 1, B 1	2, 4, 1, 6, 1, 6, 1, 2,
1572 Tyr-5 Ala-2 Tyr-8 Asn-1 Pro-1.	
167 132 - 863	
728098 16	
HDPGD34	
157	

	42-63, 12- 28	230-267, 2-18, 87- 103	88-105, 60-76
			•
1, H0555: 1, H0436: 1, H0478: 1, S0027: 1, S0028: 1, L0439: 1, L0688: 1, L0583: 1, L0362: 1, L0366: 1, H0668: 1, S0196: 1, H0542: 1, H0423: 1, S0456: 1 and S0021: 1.	AR096: 1, AR052: 1, AR104: 1, AR033: 1, AR089: 0, AR053: 0, AR055: 0, AR061: 0, AR060: 0 L0766: 5, L0748: 3, L0758: 3, L0791: 2, S0328: 2, L0747: 2, L0777: 2, H0251: 1, H0673: 1, L0803: 1, L0806: 1, L0665: 1, H0547: 1, H0436: 1, L0749: 1, L0756: 1, L0779: 1, L0759: 1, H0445: 1 and L0759: 1.	AR096: 2, AR055: 1, AR089: 1, AR033: 1, AR060: 1, AR061: 0, AR053: 0, AR039: 0, AR104: 0, AR052: 0 H0457: 1 and H0521: 1.	AR061: 0, AR060: 0, AR096: 0, AR033: 0,
	Thr-35 to Lys-40, Pro-63 to Gin-69, Leu-122 to Thr-128.	Tyr-81 to Ile-88, Ala-113 to Gin-118, Asn-183 to Ser-189.	
	1573	1574	1575
	212 - 769	157 - 972	95 - 445
	168	169	170
	728763	728861	728903
	HLYBU12	HEONV59	160 HCWHX54 728903
	158	159	160

WO 01/9030	rcin	1201/10
	103-119, 55-71	43-62, 1- 17
AR052: 0, AR039: 0, AR104: 0, AR089: 0, AR055: 0, AR053: 0 H0305: 1 and H0423: 1	AR053: 19, AR052: 17, AR089: 12, AR060: 8, AR033: 7, AR061: 5, AR104: 4, AR039: 3 L0766: 4, L0779: 4, L0803: 3, L0747: 3, L0752: 3, H0039: 2, H0059: 2, L0794: 2, S0027: 2, L0744: 2, L0740: 2, L0777: 2, L0759: 2, S0430: 1, S0418: 1, S0358: 1, S6014: 1, H0040: 1, L0776: 1, L0662: 1, L0787: 1, L0776: 1, L0384: 1, L0775: 1, L0776: 1, H0682: 1, L0787: 1, L0663: 1, H0702: 1, H0547: 1, H0682: 1, H0595: 1, S0276: 1 and H0542: 1.	AR039: 53, AR033: 27, AR096: 21, AR055: 20,
	Arg-26 to Gln-35, Arg-41 to Asn-46, Tyr-80 to Ser-85.	1577 Phe-22 to Asn-33, Ala-68 to Gly-73.
	1576	1577
	739 -	113 - 439
	171	172
	730794	730924
	HE8DF23	НОЕСО53
	161	162

WO	01	/90	304		_																·				PC'	T/U	S0:	1/16	645
		٠																											
			-			-															_							 ,	
18,	18,	15	_	0754:	•	10087:	_	0360:	_	0544:		0773:	_	0747:		0341:	_	.6900I	6	10510:		0646:		[0710:	_	0745:		0436:	
	:680	:090	766: 5,	8: 5, L	007:4	7: 4, I	776: 4	8: 4, S	245:3,	8:3, 田	1023: 3	2.3, L	655: 3,	1: 3, L	422:3	5: 2, H	549: 2	6: 2, E	150: 2	7:2, E	634: 2	3: 2, L	806: 2,	9:2,H	014: 2,	2: 2, L	755: 2,	5: 2, S	423. 2
19, AF	18, AF	15, AR	10, LO	1007	: 4, S0	, H061	4,10	1,075	3, SO(S0278	: 3, HO	S014,	3,10	1.075	: 3, HO	H029	2, H0	, H048	: 2, H0	, H005	: 2, H0	,1076	2, LO	, H053	: 2, \$3(1.074	2, LO	H04	2. H0542: 2. H0423: 2.
AR053: 19, AR104:	2052 :	AR061: 15, AR060:	S0126: 10, L0766: 5	S0027: 5, L0748: 5, L0754:	, H0484: 4, S0007: 4,	H0370: 4, H0617: 4, H0087:	4, L0803: 4, L0776: 4	.0744: 4, L.0758: 4, S0360:	S0408: 3, S0045: 3,	S0046: 3, S0278: 3, H0544:	3, H0545: 3, H0023: 3,	S0144: 3, S0142: 3, L0773:	3, L0794: 3, L0655: 3,	.0659: 3, L0751: 3, L0747:	3, H0543: 3, H0422: 3,	S0040: 2, H0295: 2, H0341:	2, S0029: 2, H0549: 2,	H0441: 2, H0486: 2, H0069:	2, H0530: 2, H0150: 2,	H0050: 2, H0057: 2, H0510:	2, H0424: 2, H0634: 2,	H0551: 2, L0763: 2, L0646:	2, L0378: 2, L0806: 2,	.0805: 2, H0539: 2, H0710:	2, H0696: 2, S3014: 2,	S0028: 2, L0742: 2, L0745:	2, L0750: 2, L0755: 2,	.0757: 2, H0445: 2, S0436:	H0542
Ā	<u>A</u>	A.	S	<u>80</u>	'n,	Ħ	4	3	ထ	80	ъ,	8	<u></u> က်	ន	က်	SO	વ	H	ъ	H	Q,	H	4	<u>3</u>	q	SO	a	2	2
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																						710 - 141 1							
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	139-168,	5-26, 90- 108, 52-72
H0144: 1, H0547: 1, H0670: 1, S0378: 1, S0152: 1, H0521: 1, H0522: 1, S3012: 1, S0206: 1, L0743: 1, L0740: 1, L0779: 1, L0731: 1, L0588: 1, L0603: 1, H0667: 1, H0216: 1, S0192: 1, S0194: 1 and S0196: 1.	AR033: 7, AR052: 2, AR089: 1, AR053: 1, AR061: 1, AR060: 1, AR104: 0, AR096: 0, AR104: 0, AR039: 0 L0769: 8, L0794: 8, L0439: 7, H0399: 3, L5565: 3, L0758: 3, H0253: 2, H0051: 2, L0438: 2, L0748: 2, L0777: 2, H0624: 1, H0441: 1, H0438: 1, L0021: 1, H0618: 1, S0049: 1, H0562: 1, S0050: 1, S0051: 1, L0638: 1, L0789: 1, H0547: 1, H0658: 1, L0743: 1, L0753: 1, S0031: 1 and S0260: 1.	AR096: 75, AR089: 75, AR039: 63, AR104: 56, AR053: 46, AR052: 36,
	Cys-30 to Tyr-36, Thr-41 to Gly-46, Val-111 to His-122, Pro-201 to Arg-206, Pro-209 to His-216.	Lys-45 to Arg-52.
	375 - 1578 1022	157 - 1579 666
	173	174 15
	731889	732236
	HDFAB91	HWLER32
	163	164

WO 01/90304	γ																	1/0	וטפ	/10	450
	43-59					<u> -</u>								·				-7			
																					-
																				,	
AR060: 31, AR033: 30, AR055: 11, AR061: 10 L0748: 3, S0354: 1, H0421: 1, H0355: 1, S0428: 1 and S0031: 1.	AR055: 9, AR052: 7, AR060: 4, AR033: 4,	AR061: 4, AR089: 3, AR096: 3, AR053: 3,	AR039: 1, AR104: 1	L0779: 3, L0755: 3, H0222:	2, H0575: 2, H0705: 2,	H0581: 2, H0622: 2, H0030:	2, L0803: 2, L0659: 2,	2 10777-2 10591-2	H0556: 1, H0159: 1, T0049:	1, H0650: 1, S0418: 1,	S0045: 1, H0437: 1, T0060:	1, H0069: 1, H0599: 1,	H0046: 1, L0163: 1, S0051:	1, H0083: 1, H0179: 1,	H0416: 1, H0039: 1, H0553:	1, H0628: 1, S0366: 1,	H0038: 1, H0551: 1, H0488:	1, H0268: 1, H0059: 1,	T0042: 1, S0422: 1, H0529:	1, L0770: 1, L0667: 1,	L0800: 1, L0641: 1, L0773:
	1580 Gln-2 to Lys-7, Glu-35 to Thr-42,	Arg-64 to Ser-72.											•								
	1580																_			·	
	29 - 430						,											-			
	175												,								
	732600	•														•					
	HNFJE71																•		•		
	165			 -															<u> </u>		

WO 01/90304		PC1/USU1/10
	103-119, 63-79	86-103, 30-46
1, L0662: 1, L0794: 1, L0766: 1, L0650: 1, L0375: 1, L0530: 1, L0791: 1, L0663: 1, S0216: 1, S0380: 1, H0521: 1, S0027: 1, L0748: 1, L0731: 1, L0757: 1, L0758: 1 and H0423: 1.	AR033: 6, AR104: 2, AR060: 1, AR052: 1, AR089: 1, AR061: 0, AR055: 0, AR039: 0, AR096: 0, AR053: 0 S0342: 1	AR050: 6, AR033: 6, AR055: 6, AR089: 5, AR056: 5, AR104: 5, AR052: 3, AR053: 3, AR061: 3, AR039: 1 H0399: 4, L0805: 3, H0661: 2, S0356: 2, H0457: 2, L0794: 2, L0775: 2, L0663: 2, L0747: 2, L0759: 2, L0005: 1, H0580: 1, S0222: 1, H0156: 1, L0021: 1, H0575: 1, H0581: 1, H0327: 1, H0123: 1, H0012: 1, H0057: 1, S0051: 1, H0328: 1, H0163: 1, H0038: 1, H0413: 1, H0100: 1,
	Phe-6 to Ser-16.	Phe-70 to Val-76.
	1581	1582
	114 - 536	248
	176	177
	732902	733800
	ноиназе	HMSHT01
	166	167

	50-66, 70- 86	194-211, 73-89	62-78, 20-
7769: 0435: 1777: and	8, 6, 4, 2, 1 1 10766:	i, i, i, i, i, i, i, i, i, i, i, i, i, i	,
S0002: 1, L0598: 1, L0769: 1, L0766: 1, L0657: 1, L0666: 1, L0665: 1, H0435: 1, S0152: 1, H0521: 1, L0740: 1, L0754: 1, L0777: 1, S0194: 1, S0276: 1 and H0542: 1.	9, AR061: 6, AR052: 5, AR089: 1, AR104: 2, H0575: 2 2, H0575: 2 1, L0803: 2, 1 1: 1, H0390: 1, L0645: 1, 1, L0747: and L0601:	AR055: 4, AR033: 3, AR096: 3, AR052: 3, AR061: 3, AR039: 2, AR060: 2, AR089: 2, AR053: 1, AR104: 1 L0783: 2, L0751: 2, H0409: 1, H0559: 1, L0471: 1, H0646: 1, H0658: 1, S0390: 1, L0777: 1, L0731: 1 and L0462: 1.	AR096: 8, AR053: 7,
8001 1, L 1, L 1, S 1, S 1, S H 1, S H		3,	
	1583 Arg-16 to Glu-27.	1584 Pro-5 to Thr-10, Lys-23 to Asn-3 Gln-105 to Tyr-	1585 Glu-40 to Tyr-45.
	178 96 - 401	880 880	180 35 - 673
	734582	735584	735747
	168 HAPQM57	169 HSLJK58	170 HSLHL67

36, 111- 127	98-116, 136-152
	,
AR060: 7, AR039: 6, AR089: 6, AR052: 6, AR055: 6, AR104: 5, AR033: 5, AR061: 4 S0280: 1, H0488: 1, H0509: 1 and S0028: 1.	AR055: 10, AR060: 7, AR033: 6, AR061: 6, AR089: 6, AR052: 4, AR089: 6, AR052: 4, AR104: 3, AR039: 2 H0052: 5, L0748: 5, L0756: 4, L0731: 4, S0360: 3, L0764: 3, L0747: 3, L0749: 3, H0255: 2, H0333: 2, L0556: 2, L0653: 2, L0740: 2, L0754: 2, L0750: 1, H036: 1, H0341: 1, H0662: 1, H036: 1, H0402: 1, H0556: 1, H0135: 1, H0556: 1, H0135: 1, L0770: 1, L0769: 1, L0630: 1, L076: 1, L0630: 1, L0776: 1, L0493: 1, H0684: 1, S0328: 1, L0775: 1, L0776: 1, L0493: 1, H0684: 1, S0328: 1, L0752: 1, L0777: 1, L0752: 1, L0758: 1, L0752: 1,
AR AR AR SI SI HO	Arg-11 to Ser-24, AR Ser-37 to Ala-43. AR
	1586 A S
	1148
	181
	738228
	HCEMF51
	[

83-102, 10-26	48-64, 121-137	47-67
AR089: 17, AR060: 15, AR096: 15, AR055: 13, AR039: 13, AR033: 12, AR104: 11, AR052: 10, AR053: 8, AR061: 7 H0318: 1 and H0063: 1.	AR061: 3, AR052: 2, AR089: 2, AR055: 2, AR033: 2, AR104: 2, AR096: 2, AR060: 1, AR053: 1, AR039: 0 L0742: 4, H0484: 2, L0763: 2, L0758: 2, H0483: 1, H0618: 1, H0047: 1, H0188: 1, S0344: 1, L0637: 1, L0771: 1, L0803: 1, L0628: 1, H0683: 1, H0522: 1 and L0752: 1.	AR089: 9, AR060: 8, AR033: 7, AR096: 2, AR053: 1, AR061: 1, AR055: 0, AR052: 0, AR039: 0, AR104: 0 L0809: 3, H0442: 2, S0010: 2, L0794: 2, L0803: 2, S0378: 2, H0341: 1, S0376: 1, H0611: 1, H0486: 1, H0013: 1, H0156: 1,
AR089: AR096: AR039: AR104: AR053: H0318:	~~~~ ~~~~~~	AR089: AR053: AR055: AR055: AR039: L0809: S0010: 2, S0378: S0376: 1, H0013 L0021: 1
·	Ser-22 to His-33, Pro-85 to Asn-94, Phe-101 to Gln-108.	Ala-9 to Leu-16.
1587	1588	1589
182 59 - 373	656	149 - 526
	183	184
738569	738911	739003
172 HTHCV59 738569	HCHCI12	174 HOEAU34
172	173	174

H. HOUGH: 1, LOTGS: 1, S0344: H. LOTGS: 1, LOT73: 1, LO			
1, 1, 10024; 1, 10333; 1, 1, 1, 10024; 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,		71-90, 13- 29, 42-58	61-78
1, H0024: 1, L0483: 1, H0163: 1, S0344: 1, L0769: 1, L0773: 1, L0769: 1, L0773: 1, L0769: 1, L0773: 1, L0774: 1, L0518: 1, S0126: 1, H0684: 1, S0380: 1, S0264: 1, H0684: 1, S0380: 1, S0265: 1, H0667: 1 and H0543: 1, L0774: 1, L0608: 1, S0265: 1, H0667: 1 and H0543: 1, L0774: 1, L0769: 1, L0774: 1, L0779: 0, AR039: 0, AR039: 0, AR039: 0, AR039: 0, AR039: 0, L0779: 1, L0630: 1, L0643: 1, L0630: 1, L0666: 1, L0438: 1, L0666: 1, L0438: 1, H0696: 1 and L0777: 1, L0779: 1, L0666: 1, L0438: 1, H0696: 1 and L0777: 1, L0779: 1, L0666: 1, L0438: 1, H0696: 1 and L0777: 1, L0779: 1, L0666: 1, L0438: 1, H0696: 1			133780, 266150, 276903, 276903, 276903
739048 185 45 - 368 1590 739503 186 152 - 1591 Lys-5 to Glu-11, 490 Tyr-17 to Asp-25.			
739048 185 45 - 368 1590 739503 186 152 - 1591	1, H0024: 1, L0483: 1, H0135: 1, H0163: 1, S0344: 1, L0769: 1, L0773: 1, L0774: 1, L0518: 1, S0126: 1, H0684: 1, S0380: 1, S0454: 1, H0436: 1, L0754: 1, L0747: 1, L0608: 1, S0026: 1, H0667: 1 and H0543: 1.	AR104: 1, AR061: 1, AR060: 0, AR039: 0, AR033: 0, AR089: 0 L0734: 3, L0749: 2, L0731: 2, H0650: 1, S0408: 1, S0300: 1, L0456: 1, L0769: 1, L0637: 1, L0643: 1, L0650: 1, L0659: 1, L0792: 1, L0666: 1, L0438: 1, H0696: 1 and L0747: 1.	AR055: 6, AR096: 5, AR052: 5, AR060: 4, AR089: 4, AR061: 4, AR053: 4, AR033: 3, AR104: 1, AR039: 0 L0362: 20, L0766: 11, L0754: 10, L0747: 5, L0731: 4, S0003: 3, H0547: 3, S0026: 3, S0212: 2, H0251: 2, H0046: 2, H0031:
739048 185 45 - 368 739503 186 152 - 490			Lys-5 to Glu-11, Tyr-17 to Asp-25.
739048 185		1590	1591
739048	,	45 - 368	152 - 490
		185	186
		739048	739503
175		HFASN59	
	•	175	176

, 46-68, 21-	42, 66-82,
į	
2, H0674: 2, L0769: 2, L0438: 2, L0438: 2, L0448: 2, L0439: 2, L0448: 2, L0439: 1, H0686: 1, T0049: 1, S0134: 1, H0657: 1, S0001: 1, H0459: 1, H0459: 1, H0459: 1, H0459: 1, H0459: 1, H0469: 1, H0568: 1, H0571: 1, H0569: 1, H0569: 1, H0569: 1, L0649: 1, L0779: 1, L0664: 1, H0519: 1, L0779: 1, L07	
1592 Ala-87 to Ala-97.	
	1/21
2615 -	2247
187	2
HSDIN50 740786	3
9	-
	1

VO 01/90304	PCT/US01/16450
	89-106, 40-56
	·
AR104: 4, AR060: 3, AR039: 3, AR055: 3, AR061: 2, AR033: 1 L0005: 4, S0045: 4, S0222: 4, S0028: 4, H0624: 3, S0144: 2, S0260: 2, S0134: 1, S0218: 1, H0381: 1, H0341: 1, S0001: 1, S0282: 1, S0046: 1, L0476: 1, H0191: 1, H0575: 1, S0050: 1, H0048: 1, H0135: 1, S0038: 1, H0100: 1, S0150: 1, L0378: 1, S0390: 1 and S0041: 1,	AR052: 11, AR053: 9, AR033: 7, AR096: 7, AR104: 6, AR089: 6, AR060: 4, AR055: 3, AR061: 2, AR039: 2 S0354: 5, S0426: 5, S0002: 3, S0278: 2, L0375: 2, L0751: 2, L0758: 2, L0539: 1, H0392: 1, H0592: 1, H0318: 1, L0041: 1, H0494: 1, S0144: 1, S0142: 1, S0344: 1, L0803: 1, L0804: 1, L0805: 1, L0776: 1, S0052: 1, S0428: 1, S0053: 1, H0144: 1, S0378: 1,
A A A L A Q TH TH TH Q TO Q	Ser-23 to Lys-37, A Thr-61 to Pro-66. A A A A A A A A A A A A A A A A A A A
	803 803
	188 43
	5 741055
	HMAFM05
	178

								23					<u></u>								6		_				
	61-78						73-89,	109-125						_							611-66		_				
	133780, 266150,	276903	276903,	276903																							
	11q13.5						61																				
78: 1.	19, 3,	. 2,	. 2,		1		.1,		.; O	ő	0	2,	, H0329:	‡: 1,	,1064	; 1,	, L0805:	.1,	1, 1.0786:	601: 1.	6: 39,	9: 33,	2: 23,	3: 20,	1: 6	1 and	
H0555: 1 and H0478: 1.	AR053: 24, AR052: AR096: 7, AR089:	2, AR039:	2, AR060:	1, AR061	H0486: 1 and H0494: 1		2, AR060:	1, AR104:	1, AR055:	0, AR052:	4R039: 0, AR053:	L0766: 2, L0776: 2,	0759: 2, T0002: 1, H0329:	1, H0604: 1, H0424: 1,	S0144: 1, L0800: 1, L0644:	I, L0662: 1, L0804: 1	.0775: 1, L.0806: 1, L.0805:	, L0659: 1, H0593: 1,	H0539: 1, H0521: 1, L0786:	, L0731: 1 and L0601: 1	AR104: 74, AR096: 39,	34, AR03	AR033: 24, AR052: 23,	23, AR05	AR055: 11, AR061: 6	S0010: 1, L0740: 1 and	
H0555: 1	AR053: AR096:	AR033:	AR104:	AR055:	H0486:		AR096:	AR089:	AR033:	AR061:	AR039:	10766:	1.0759: 2,	1, H0604	S0144: 1,	1, L0662	1.0775: 1,	1, L0659	H0539: 1	1, L0731	AR104:	AR089:	AR033:	AR060:	AR055:	S0010:	1.0752: 1.
	Lys-5 to Glu-11, Tyr-17 to Asp-25,	Lys-39 to Ile-45,	Val-81 to Leu-93,	Thr-100 to Phe-106,	Thr-117 to Glu-126,	Thr-128 to Gln-133.	Leu-44 to Glu-49,	Tyr-61 to Cys-68,	Glu-94 to Ile-108.												1596 Pro-6 to Thr-21,	Asp-47 to Ile-57,	Lys-76 to Tyr-90.				,
	1594						1595														1596						
	139 - 555						19 - 483														112 -	492					
	189						190														191						
	741128						741659														741921		,				
	HKAAA18					,	HISCL61														HAGDA61						
	179						180														181						

62-78, 92- 108	54-71, 133-149	55-71, 24 40, 74-90
AR096: 5, AR089: 3, AR106: 3, AR033: 2, AR104: 2, AR052: 1, AR039: 1, AR053: 1, AR055: 1, AR061: 1 H0038: 3, L0439: 3, H0039: 2, L0740: 2, L0747: 2, L0756: 2, H0592: 1, H0318: 1, H0031: 1, H0644: 1, L0766: 1, L0774: 1, L0666: 1, L0438: 1, L0754: 1, L0779: 1, L0758: 1, S0192: 1, S0194: 1 and H0506: 1.	AR053: AR052: AR053: AR060: AR061: L0748: H0046: 1 1, H0412: H0520: 1 H0543: 1	AR033: 7, AR060: 5, AR089: 5, AR061: 2, AR039: 2, AR096: 1, AR055: 0, AR053: 0, AR052: 0
1597 Met-1 to Gly-7, Ala-16 to Gln-21, Ser-35 to Gly-41, Thr-43 to Asn-52.	Glu-4 to Gly-12, Gly-19 to Ser-37, Gln-49 to Asn-54, Glu-102 to Cys-108, Leu-116 to Asn-125.	Ser-43 to Val-53.
1597	1598	1599
209	46 - 840	101 - 442
261	193	1 8
742518	742690	743383
HFIIO11	HUSGB32	HTXED15
182	183	184

		<u> </u>	
	75-91	128-146, 21-37, 63- 79	96-124
		601843	108725, 120700, 133171, 136836, 145981, 147141,
		19p12	19p13.3
H0265: 1, H0556: 1, H0026: 1, L0522: 1, L0665: 1 and H0445: 1.	AR052: 3, AR089: 2, AR033: 2, AR053: 2, AR060: 2, AR055: 1, AR096: 1, AR104: 1, AR061: 1, AR039: 0 H0521: 2, H0305: 1, H0046: 1, S0144: 1, S0002: 1, H0478: 1, L0748: 1, H0543: 1, H0423: 1 and H0542: 1.	AR055: 20, AR039: 13, AR052: 13, AR053: 11, AR061: 11, AR096: 10, AR033: 10, AR089: 9, AR060: 9, AR104: 7 H0428: 2, H0135: 2, L0794: 2, L0779: 2, L0770: 1, L0766: 1, L0774: 1, L0789: 1, L0792: 1, L0439: 1, L0731: 1 and L0757: 1.	AR053: 1, AR096: 1, AR055: 1, AR052: 1, AR089: 1, AR033: 1, AR061: 1, AR060: 1, AR104: 0, AR039: 0 L0747: 5, L0809: 3,
	·	,	1602 Gly-14 to Gly-23.
	1600	1601	1602
	25 - 333	55 - 573	201 - 611
	195	196	197
	743426	744278	744330
	HCFMF12	HSSJG62	HFTHF63
	185	186	187

W U 01/90304		PC 1/USU1/16
	115-131	71-99, 22- 50
164953, 188070, 600957, 601238, 601846, 602216,	·	
59: 3, L0777: 0021: 1, 52: 1, L0770: 0792: 1, 50: 1, L0779: d S0194: 1.	AR033: 1, AR089: 0, AR061: 0, AR096: 0, AR060: 0, AR053: 0, AR104: 0, AR052: 0, AR104: 0, AR039: 0 L0372: 2, L0748: 2, L0372: 2, L0754: 2, L0779: 2, L0756: 2, L0779: 2, L0755: 2, H0170: 1, S0212: 1, S0282: 1, H0346: 1, S0376: 1, S0360: 1, T0040: 1, H0253: 1, H0424: 1, H0553: 1, H0674: 1, L0772: 1, L0764: 1, L0771: 1, L0764: 1, L0771: 1, L0764: 1, L0771: 1, L0764: 1, L0771: 1, L046: 1, L0771: 1, L0477: 1.	1, AR089: 1, 1, AR039: 0, 0, AR053: 0, 0, AR060: 0, 0, AR055: 0
L0731: 3, L0759: 3, L0777: 2, L0752: 2, L0021: 1, S0250: 1, H0252: 1, L0770: 1, L0774: 1, L0792: 1, L0793: 1, L0750: 1, L0779: 1, L0758: 1 and S0194: 1.		AR096: 1, AR089: AR033: 1, AR039: AR061: 0, AR053: AR104: 0, AR060: AR052: 0, AR055:
	Tyr-9 to Asn-15, Arg-57 to Trp-64, Pro-68 to Ala-78, Gln-83 to Asp-88, Pro-106 to Ser-112.	
	1603	1604
	759 - 1223	234 - 584
	198	199
	744453	744616
	HMDAG54 744453	HCHMI51
	188	189

W U 01/90304		0201/10
	84-100	76-107, 1- 17, 114-
1, L0540: 1, L0383: 1, L0790: 1, L4508: 1, H0658: 1, H0650: 1, H0672: 1, H0651: 1, S0330: 1, S0378: 1, S0332: 1, S0013: 1, H0696: 1, S0392: 1, H0627: 1, H0445: 1, H0667: 1, H0542: 1, S0452: 1, L0600: 1 and H0352: 1.	AR033: 38, AR089: 32, AR052: 29, AR104: 27, AR096: 27, AR060: 22, AR053: 22, AR055: 11, AR039: 11, AR061: 9 H0599: 5, H0575: 3, L0438: 2, S0212: 1, S0420: 1, S0356: 1, H0393: 1, H0549: 1, H0391: 1, H0036: 1, T0071: 1, H0581: 1, S0051: 1, H0266: 1, H0571: 1, H0292: 1, H0272: 1, L0435: 1, H0435: 1, H0521: 1, S0028: 1, L0439: 1, H0547: 1, H0543: 1 and H0542: 1, H0543: 1 and	AR039: 12, AR096: 7, AR104: 7, AR033: 6,
		1606 Ser-21 to Trp-28, Arg-63 to Val-68.
	1605	1606
	220 - 531	108 - 500
	200	201
	744726	744831
·	190 НАНВА63	HAJAN63
	061	191

V 0 01/2000	101,0001,10100
130	256-273, 42-58
AR060: 5, AR089: 4, AR052: 4, AR053: 4, AR055: 4, AR061: 3 H0616: 3, L0748: 3, L0756: 3, H0586: 2, H0356: 2, L0766: 2, L0803: 2, H0672: 2, L0439: 2, L0758: 2, L0465: 2, H0497: 1, H0013: 1, H0046: 1, L0471: 1, H0024: 1, S0214: 1, H0124: 1, H0561: 1, L0774: 1, L0664: 1, L0438: 1, H0520: 1, H0519: 1, H0658: 1, H0539: 1, H0631: 1, L0740: 1, L0747: 1, L0755: 1, L0595: 1, S0192: 1, S0276: 1 and H0352: 1.	AR055: 10, AR060: 5, AR053: 5, AR052: 5, AR033: 5, AR061: 4, AR089: 4, AR096: 4, AR104: 2, AR039: 0 S0022: 7, L0805: 3, H0556: 2, H0046: 2, L0764: 2, L0662: 2, S0126: 2, L0748: 2, H0305: 1, H0013: 1, H0050: 1, H0615: 1, H0039: 1, H0640: 1, H0087: 1, T0042: 1, L0643: 1,
A A A A A A A A A A A A A A A A A A A	Pro-27 to Arg-42, AR Asp-94 to Ser-104, AR Arg-114 to Asn-120, AR Ala-127 to Ala-138, AR Ala-156 to Pro-163, AR Gln-231 to Leu-238. St H00 L07 L07 L07 L07 L07 L07 L07 L07 L07 L
	1607
	368 - 1276
	202
	745408
	HSRFP52
	192

VO 01/90304	,					· · · · ·				1/050	1/1045
··	177-195, 53-69, 150-166,	16-32									
<u> </u>											
								••	••		
1, L0807: 1, L0809: 1, L0666: 1, H0144: 1, H0547: 1, L0749: 1, L0779: 1 and L0758: 1.	1	AR039: 3, AR060: 3, AR055: 1, AR061: 1 S0001: 4, L0439: 4,	3, L0748: 3, H0484: 2, S0420: 2, S0222: 2, H0274:	2, H0181: 2, H0529: 2, L0517: 2, L0789: 2, H0659: 2, L0751: 2, L0596: 2	L0361: 2, H0295: 1, T0049: 1, H0656: 1, S0418: 1,	L0005: 1, S0476: 1, H0645: 1, H0333: 1, L0021: 1,	H0036: 1, H0052: 1, H0597: 1, H0545: 1, H0009: 1,	H0178: 1, H0081: 1, S0388: 1, H0673: 1, S0036: 1,	H0038: 1, H0494: 1, L0769: 1, L0796: 1, L0796: 1, L0372: 1.	L0800: 1, L0643: 1, L0645:	1, 10805: 1, L0792: 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,
	1608 Gly-7 to Lys-16, Gly-84 to Pro-90, Pro-100 to Ser-106.										
	1608										
	140 - 904										
	203										
	746390										
	нснон38										
	193						-				

	201-217
	·
1, S0328: 1, H0547: 1, H0547: 1, S0328: 1, H0696: 1, S0406: 1, S0028: 1, S0032: 1, L0742: 1, L0779: 1, L0777: 1, L0780: 1, L0757: 1, L0592: 1, L0595: 1, S0026: 1 and H0423: 1.	AR052: 11, AR053: 10, AR096: 9, AR055: 7, AR033: 6, AR060: 5, AR039: 5, AR061: 4, AR039: 4, AR104: 4 L0748: 14, H0457: 9, L0766: 8, H0543: 7, L0731: 6, L0439: 5, L0770: 4, L0747: 4, H0542: 4, S0002: 3, L0777: 3, H0445: 3, S0434: 3, S0192: 3, H0423: 3, S0114: 2, H0575: 2, S0010: 2, L0667: 2, L0646: 2, L0775: 2, L0655: 2, H0436: 2, L0749: 2, L0594: 2, H0420: 2, S0342: 1, S0134: 1, H0583: 1, S0212: 1, S0376: 1, S0476: 1, S0222: 1, H0486: 1, H0635: 1, H0156: 1, S0346: 1, S0474: 1, H0263: 1, H0572: 1,
	Thr-17 to Glu-25, Glu-61 to Val-66, Leu-122 to Cys-129, Glu-139 to Asp-148, Pro-169 to Val-179, Lys-183 to Gly-193. I series to Gly-194. I series to Gly-194. I series to Gly-195. I series to Gly-195. I series to Gly-196. I series to Gly-196
	1609
	783 - 1
	200
	746583
	HMSBS61
	194

WO 01/90304	PC 1/USU1/10450
	180-197
	·
	-
H0050: 1, H0687: 1, S0214: 1, L0483: 1, H0032: 1, S0364: 1, L0455: 1, H0708: 1, H0591: 1, H0591: 1, H0641: 1, H0529: 1, L0776: 1, L0771: 1, L0652: 1, L0774: 1, L0805: 1, L0774: 1, L0540: 1, L0776: 1, L0593: 1, L0789: 1, L0790: 1, L0793: 1, L0665: 1, H0144: 1, H0547: 1, H0672: 1, H0539: 1, S0152: 1, L0750: 1, L0757: 1, L0758: 1, S0308: 1, S0011: 1, S0242: 1 and H0771: 1	AR055: 9, AR060: 5, AR052: 5, AR061: 4, AR033: 4, AR096: 3, AR104: 1, AR039: 1 H0521: 3, L0731: 3, H0591: 2, H0436: 2, H0422: 2, H0170: 1, S0001: 1, H0459: 1, S0046: 1, S0476: 1, H0610: 1, H0013: 1, H0635: 1, H0271: 1, H0622: 1, H0560: 1, H0699: 1, S0152: 1, L0747: 1, S0434:
	Met-1 to Ser-7.
	1610
	195 - 908
	205
	746584
	HNFHK32
	195

WO 01	/9030	4		_							_											I	·C1	WU.	S01	/164
	106-122									109-125,	6-22					62-96, 17-	48, 89-105					112-128,	56-72			
				-														<u>.</u>								
pu						10:		31:	1.						•					a da dassi		- 5		<u></u>		
1, L0601: 1, H0542: 1 and H0543: 1.	AR053: 21, AR052: 15,	AR060: 10, AR055: 9,	9, AR104: 7,		H0486: 2, L0747: 2,	S0298: 1, H0392: 1, T0010:	l, H0039: 1, H0529: 1,	L0766: 1, L0438: 1, L0731:	1, L0591: 1 and H0543:	AR089: 1, AR096: 0,	0, AR052: 0,	0, AR061: 0,			H0013: 2 and S0218: 1	l.					: 2	AR055: 12, AR060: 12,	9, AR033: 8,			4, AR039: 4
1, L0601 H0543: 1	AR053:	AR060:	AR033:	AR061:	H0486	S0298:	1, H003	10766:	1, 1.059	AR089:	AR060:	AR104:	AR053:	AR039:	H0013	AR055:	AR052:	AR096:	AR033:	AR089:	H0040: 2		4, AR061:	7, AR104:	AR089:	AR052:
	Tyr-14 to Glu-19,	Lys-46 to Asp-21.						•							,							1614 Cys-175 to Val-181,	Lys-184 to Arg-204, AR061:	Gln-218 to Glu-227,	Lys-233 to Phe-242. AR089:	
	1611									1612						1613						1614				
	53 - 556									470 - 72						117 -	434					2-751				
	206	-								207						802						8				
	747208		•							750243						750750						751048				
	HTPCT63									HE8NL29						HITTFM66						HE9EM20				
	196									197						198						199				

	FC1/0501/10450
	193-218, 30-46
L0803: 8, L0748: 7, L0759: 5, L0588: 3, H0489: 2, L0105: 2, L0659: 2, L0666: 2, H0144: 2, H0520: 2, H0547: 2, L0439: 2, L0754: 2, L0747: 2, L0756: 2, L0752: 2, S0360: 1, L0717: 1, H0611: 1, H033: 1, H0046: 1, T0010: 1, H0428: 1, H0031: 1, H0553: 1, H0644: 1, S0366: 1, H0652: 1, L0372: 1, L0646: 1, L0652: 1, L0776: 1, L0641: 1, L0774: 1, L0776: 1, L0779: 1, L0731: 1, S0343: 1, L0779: 1, L0731: 1, S0343: 1, L0731: 1, L0779: 1, L0731: 1, S0343: 1, L0731: 1, L0779: 1, L0731: 1, S0434: 1, L0596: 1 and L0604: 1, L0506: 1 and L0604: 1, L0506: 1 and L0604: 1, L0731: 1, S0434: 1, L0596: 1 and L0604: 1, L0731: 1,	AR096: 12, AR089: 9, AR033: 5, AR052: 5, AR039: 5, AR060: 4, AR104: 3, AR053: 2, AR061: 1, AR055: 1 S0410: 4, H0660: 4, S0354: 2, H0370: 2, L0662: 2, L0438: 2, L0748: 2, H0664: 1, S0360: 1, H0208:
	Lys-12 to Glu-27, Pro-48 to Lys-56.
	1615
	832 832
	210
	751286
	HISCQ44
	200

.,	PC1/USU1/10450
	175-192, 94-110
1, H0574: 1, H0575: 1, H0590: 1, L0040: 1, H0051: 1, H0169: 1, H0674: 1, H0412: 1, L0645: 1, L0767: 1, L0666: 1, L0665: 1, H0547: 1, H0539: 1, H0478: 1, L0611: 1, L0741: 1, L0750: 1 and S0434: 1.	AR055: 8, AR053: 6, AR052: 6, AR033: 6, AR060: 5, AR089: 5, AR096: 4, AR061: 4, AR039: 3, AR104: 3 H0551: 3, H0529: 3, L0770: 3, L0769: 3, L0794: 3, L073: 2, L0769: 2, H0701: 2, S0126: 2, L0747: 2, L0731: 2, L0521: 2, H0701: 2, S0126: 2, L0747: 2, L0731: 2, L0521: 2, H0701: 1, S0134: 1, H0556: 1, H0592: 1, S0134: 1, H0583: 1, H0661: 1, S0476: 1, H0512: 1, H0412: 1, S0438: 1, S0440: 1, S0144: 1, L0763: 1, L0645: 1, L076: 1, L0766: 1, L0775: 1, L0783: 1, L0665: 1, H0519: 1,
	Ala-10 to Glu-18, Arg-26 to Arg-31, Phe-48 to Gln-53, Gly-77 to Glu-84, Met-130 to Gly-138, Tyr-225 to Ala-232. I 1 I 1 I 2 I 3 I 3 I 4 I 5 I 7 I 7 I 7 I 7 I 7 I 8 I 8 I 8
	1616
	203 -
	7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7
	751677
·	HTGAU79
	201

	69-103, 90-106, 1- 17	<i>57-7</i> 6, 114-130

H0435: 1, H0672: 1, H0436: 1, S3014: 1, S0028: 1, L0750: 1, L0777: 1, S0436: 1, L0366: 1, H0667: 1 and H0423: 1.	AR055: 3, AR033: 2, AR104: 2, AR060: 2, AR053: 2, AR039: 2, AR089: 1, AR061: 1, AR096: 1, AR052: 0 H0046: 2, H0431: 1, S0428: 1 and H0660: 1.	AR096: 8, AR052: 7, AR039: 6, AR053: 6, AR033: 5, AR089: 4, AR055: 4, AR104: 3, AR061: 3, AR060: 3 H0618: 9, L0751: 7, L0754: 6, L0758: 6, H0253: 5, L0748: 5, L0439: 5, H0580: 3, H0052: 3, L0770: 3, L0663: 3, H0556: 2, S0418: 2, H0733: 2, H0351: 2, H0706: 2, H0567: 2, H0625: 2, S0144: 2, S0142: 2, L0659: 2, L0543: 2, L5623: 2, L0749: 2, S0436: 2, H0423: 2, H0381: 1, S0212: 1, H0254: 1, H0663:
H0435: 1, 1, S3014: L0750: 1, L0366: H0423: 1		AR039: AR033: AR033: AR033: AR055: AR061: L0754: 6 5, L0748: 2, H0706 L0625: 2 2, L0659 L5623: 2 2, H0423 2, H0423
	Pro-26 to Pro-31, Pro-119 to Asp-124, Gln-132 to Leu-140, Arg-143 to Pro-149.	·
	1617	1618
	17 - 463	64 - 456
	212	213
	751735	752630
-	HETAJ12	HDABX16
	202	203

	110-136
	131400,
	5q31.1
1, H0638: 1, S0045: 1, S0046: 1, S0046: 1, S0476: 1, S6022: 1, H0549: 1, H0549: 1, H0549: 1, H0549: 1, H0520: 1, H0574: 1, L0622: 1, L0623: 1, H0194: 1, H0194: 1, H0194: 1, H0596: 1, H0194: 1, H0596: 1, H0570: 1, H0510: 1, H0628: 1, H0510: 1, H0551: 1, H0628: 1, H0531: 1, H0551: 1, H0631: 1, L0371: 1, L0371: 1, L0494: 1, L0497: 1, L0497: 1, L0497: 1, L0497: 1, L0497: 1, L0593: 1, H0626: 1, H0520: 1, H0520: 1, H0520: 1, H0520: 1, H0539: 1, H0520: 1, H0520: 1, H0539: 1, H0520: 1, H0539: 1, H0553: 1, H0656: 1, L0779: 1, L0593: 1, H0667: 1, L05	AR033: 12, AR055: 11,
	Asp-20 to Glu-26,
	1619
	27 - 458
	214
	753105
	HFEBM11
	204

	76-93, 38- 54	108-139	46-63
147061, 147575, 147575, 147575, 153455, 159000, 181460, 600807, 601596, 602089			
AR089: 10, AR052: 9, AR061: 9, AR053: 8, AR060: 8, AR096: 4, AR039: 3, AR104: 0 H0081: 1, H0509: 1 and S0330: 1.	AR052: 297, AR053: 285, AR096: 212, AR039: 173, AR089: 146, AR055: 106, AR104: 92, AR060: 90, AR061: 69, AR033: 67 H0169: 4, L0529: 2, H0624: 1, H0341: 1, H0333: 1, H0013: 1, H0266: 1, H0674: 1, H0269: 1, S0440: 1, L0770: 1, L0809: 1,	AR104:1068, AR061: 633, AR060: 627, AR055: 507, AR033: 469, AR089: 444, AR052: 279, AR039: 276, AR096: 237, AR053: 231 H0069: 5 and H0634: 1.	AR104: 18, AR033: 16, AR055: 9, AR060: 7,
Asp-48 to Tyr-57, Al Asn-59 to Gly-66, Al Ala-69 to Gly-76, Al Ser-91 to Asn-97. Al Scr-91 to Asn-97. Al Str-91 to Asn-97. Al Str-91 to Asn-97. Al Str-91 to Asn-97.	Ser-26 to Asn-35, Gly-95 to Pro-100, Arg-115 to Gln-126, Arg-132 to Asp-137, Val-183 to Ser-188.	Ser-50 to Thr-55, Ser-67 to Asp-72, Ala-105 to Ser-110, Gin-139 to Lys-149, Arg-152 to Ser-166.	1622 Gly-15 to His-27, A Pro-35 to Ser-44. A
	979 - 1620	456 - 1621 959	9 - 317 162
	753235 215	753289 216	754184 217
	HHGBS74 753	HTAAT39 753	207 HHSFO30 75
	205	206	207

			., <u> </u>
	55-74, 88- 104	324-340, 235-251, 64-80, 344-360	100-130,
AR061: 7, AR052: 6, AR089: 6, AR053: 4, AR096: 4, AR039: 4 L0471: 1, S0388: 1, H0633: 1 and L0591: 1.	AR061: 6, AR096: 6, AR060: 6, AR089: 6, AR039: 6, AR033: 5, AR052: 5, AR055: 5, AR053: 4, AR104: 4 H0069: 3, L0794: 1, L0803: 1 and L0758: 1.	AR053: 11, AR096: 9, AR052: 8, AR089: 6, AR104: 6, AR089: 6, AR055: 4, AR039: 4, AR033: 4, AR039: 4, AR031: 2, H0170: 1, S0134: 1, H0662: 1, S0354: 1, H0580: 1, H0619: 1, S0278: 1, H0574: 1, H0599: 1, H0590: 1, H0596: 1, LO471: 1, H0024: 1, H0014: 1, L0163: 1, H0644: 1, H0551: 1, S0002: 1, H0658: 1, L0602: 1, H0522: 1, S3014: 1, L0731: 1, L0601:	AR055: 10, AR089: 8,
	Lys-11 to Glu-29.	1624 Asp-44 to His-54, Gly-92 to Lys-98, Gln-110 to Gly-115, Tyr-135 to Gly-140, Gly-162 to Ala-167.	
	1623	1624	1625
	34 - 366	218 -	337 -
	218	219	220
	754529	756579	756676
	HTAFE69	HMSCM47	HETLM70
	208	209	210

VO 01/90304	PCT/US01/16450
1-21, 161- 192, 63- 80, 44-60	95-111
8, 7, 55, 33 00517: 00046: 10673: 0805: 00665: 00754:	5, 2, 2, 0747:
AR053: 8, AR053: 8, AR052: 7, AR061: 7, AR060: 5, AR039: 5, AR096: 4, AR104: 3 L0803: 3, S0406: 3, H0356: 2, L0800: 2, L0517: 2, L0666: 2, L0751: 2, L0779: 2, S0434: 2, L0601: 2, H0661: 1, S0442: 1, S0358: 1, S0444: 1, H0046: 1, H0150: 1, H0188: 1, H0617: 1, L0775: 1, L0805: 1, L0672: 1, L0793: 1, L0665: 1, H0689: 1, H0648: 1, S0328: 1, R0658: 1, H0648: 1, S0328: 1, S0330: 1, S0380: 1, H0696: 1, S0146: 1, L0754: 1, L0752: 1 and H0506: 1.	AR089: 5, AR052: 5, AR033: 4, AR053: 4, AR096: 3, AR061: 3, AR104: 2, AR060: 2, AR055: 2, AR039: 2 H0556: 4, H0169: 3, L0766: 3, L0742: 3, L0747: 3, S0360: 2, S0046: 2, H0587: 2, L0483: 2, T0006:
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	Leu-64 to Ala-75. ARI ARI ARI HG LO7 LO7 HO5
,	1626 Leu-64 t
1080	21 - 407
	756950 221
	1 HLYEN32
	211

VO 01/90304 PC1/	US01/1645
	83-99, 111-127
2, H0488: 2, H0059: 2, L0646: 2, S0404: 2, L0748: 2, L0439: 2, L0751: 2, H0542: 2, H0265: 1, S0040: 1, H0341: 1, S0444: 1, S0045: 1, S0132: 1, S0222: 1, H0438: 1, S0246: 1, H0052: 1, H0438: 1, S0246: 1, H0599: 1, S0346: 1, H0052: 1, H0014: 1, L0163: 1, H0083: 1, H0687: 1, S0250: 1, H0623: 1, H0639: 1, L0455: 1, H0640: 1, H0551: 1, H0623: 1, H0640: 1, L0659: 1, L0787: 1, L0793: 1, L0666: 1, L0664: 1, L0659: 1, H0519: 1, S0126: 1, H0682: 1, H0672: 1, H0520: 1, H0519: 1, S0126: 1, H0682: 1, H0436: 1, S0028: 1, L0754: 1, L0750: 1, L0756: 1, L0759: 1, H0445: 1, S0436: 1, L0759: 1, H0445: 1, S0436: 1, L0759: 1, H0445: 1, S0436:	AR033: 2, AR089: 2, AR061: 1, AR060: 1, AR096: 0, AR039: 0,
	1627 Gly-9 to Leu-25.
·	1627
	234 - 659
	222
	757207
	ннғни45
·	212

VO 01/90304		PCT/US01/164
	156-172, 186-204, 85-101	59-76, 26- 42
4 ++	.:	
1, H0052: 1, H0135: 1, H0063: 1, H0494: 1, L0794: 1, L0649: 1, S0037: 1, L0439: 1, L0747: 1, S0434: 1 and H0506: 1.	AR061: 1, AR096: 1, AR053: 0, AR089: 0, AR033: 0, AR089: 0, AR039: 0, AR065: 0, AR052: 0, AR104: 0 H0031: 3, L0800: 3, L0794: 3, L0666: 2, L0751: 2, H0265: 1, S0376: 1, H0559: 1, H0548: 1, H0156: 1, L0021: 1, H0599: 1, S0049: 1, H0545: 1, H0213: 1, H0059: 1, L0761: 1, L0649: 1, L0803: 1, L0655: 1, L4507: 1, H0723: 1, H0593: 1, H0539: 1, H0522: 1, L0756: 1, L0779: 1, L0756: 1, L0096: 1 and H0506: 1.	AR053: 9, AR052: 8, AR089: 6, AR055: 5, AR033: 5, AR096: 4, AR060: 3, AR061: 3, AR039: 2, AR104: 1 H0638: 5, L0761: 4,
	Ser-63 to Glu-72, Asn-123 to Thr-130, Pro-209 to Pro-215.	
	1629	1630
	891	87 - 437
	724	225
		757601
	HDPPA45	215 HMAGC74 757601
	214	215

226 37 - 813 1631 Ser-51 to Phe-57. AR053: 4, AR096: 3, AR089: 3, AR089: 3, AR089: 3, AR089: 3, AR089: 3, AR089: 2, AR089: 2, AR089: 2, AR089: 2, L0063: 2, L0063: 2, L0078: 1, H0070: 1, H0070: 1, H0078: 1, H0078: 1, H0078: 1, H0078: 1, L0078: 1, L0078: 1, L0062: 1, L0079: 1, L0059: 1, L0062: 1, L0079: 1, L0059: 1, L0079: 1,		
HHFFR79 759851 226 37 - 813 1631 Ser-51 to Phe-57.	238-254	259-293, 138-159, 36-57, 102-127, 235-252, 70-86, 325-341
HHFFR79 759851 226 37 - 813 1631 Ser-51 to Phe-57.	·	
HHFFR79 759851 226 37 - 813 HMGBP83 759888 227 162 - 1289	AR053: 4, AR052: 4, AR055: 4, AR096: 3, AR089: 3, AR033: 3, AR080: 3, AR033: 3, AR104: 2, AR039: 0 H0657: 2, H0485: 2, L0163: 2, H0356: 2, H0488: 2, L0763: 2, L0637: 2, L0646: 2, L0766: 2, L0754: 2, L0756: 2, L0591: 2, T0002: 1, H0497: 1, H0036: 1, H0644: 1, L0142: 1, H0628: 1, S0438: 1, H0509: 1, S0422: 1, L0665: 1, L0794: 1, L0655: 1, L0657: 1, L0382: 1, L0665: 1, H0682: 1, R0659: 1, S0378: 1, S0146: 1, S0406: 1, L0779: 1, L0596: 1, S0106: 1, S0011: 1, S0242: 1, H0543: 1 and S0424: 1.	AR055: 6, AR060: 4, AR061: 3, AR089: 3, AR033: 3, AR052: 2, AR053: 2, AR096: 2, AR104: 2, AR039: 1 S0376: 1, H0580: 1, H0614: 1, H0284: 1, H0268:
HHFFR79 759851 226 37 - 813 HMGBP83 759888 227 162 - 1289	Ser-51 to Phe-57.	Lys-7 to Pro-14.
HHFFR79 759851		
HHFFR79 HMGBP83	226 3	722
216 HHFFR79 217 HMGBP83	759851	
216	HHFFR79	HMGBP83
	216	

	7-37, 31- 51. <i>6</i> 7-90.	105-121								72-101,	32-53					57-73, 4	82					103-119		
1, H0412: 1, H0623: 1, T0042: 1, S0126: 1, H0539: 1, H0521: 1 and L0779: 1.	AR061: 6, AR055: 4, AR060: 3, AR033: 3.	AR039: 3, AR052: 3,	AR089: 3, AR096: 2,	L0749: 5, L0752: 5,	L0748: 4, H0510: 2, S0440:	2, L0800: 2, S0436: 2,	H0294: 1, H0393: 1, L0803:	1, L0774: 1, L0383: 1,	L0789: 1 and L0779: 1.	AR039: 6, AR053: 4,	AR089: 3, AR104: 3,	AR096: 3, AR052: 3,	AR033: 2, AR055: 2,	AR060: 2, AR061: 2	H0580: 1 and L0601: 1.	AR039: 25, AR096: 18,	AR089: 18, AR053: 12,	AR060: 11, AR104: 11,	AR052: 10, AR033: 10,	AR055: 6, AR061: 3	S0050: 1 and H0555: 1.	AR089: 1, AR060: 1,	AR033: 1, AR053: 0,	AR039: 0, AR096: 0,
	Phe-60 to Gly-67.																					1636 Met-1 to Glu-9,	Ser-18 to Ile-26.	
	1633									1634						1635						1636		
	179 -									90 - 392						146-	457					20 - 460		
	228									229						230						231		
	760121									760146						760240						760321		
	HAUBV24 760121	_								HWBAQ71 760146	,			-		HRACE71					_	HADGC71 760321	· · · · · · · · · · · · · · · · · · ·	
	218		····							219						220						221		

VO 01/90	304																						'C'I	7U	501	/164	450
	82-107										·—,																
																						,					
_, _		·					1777	-			426:)556:		1376:		0599:		1296:		051:		0032:		0551:		763:
R104: 0, AR052: 0, R104: 0, AR055: 0 H0427: 1 and H0328: 1	7, AR096: 6		-	3, AR104: 2	4KU01: 2, AKU39: 1 UM51: 5 UM543: 5	: 3, mo343: 3,	HU624: 4, HUI /U: 4, SU222:	4, HUU13: 3, SUUU3: 3,	H0615: 3, H0519: 3, T0049:	2, H0051: 2, H0553: 2,	H0131: 2, S0422: 2, S0426:	2, H0659: 2, L0752: 2,	S0026: 2, H0171: 1, H0556:	1, H0686: 1, H0650: 1,	S0116: 1, H0671: 1, S0376:	1, S0046: 1, H0369: 1,	H0497: 1, H0156: 1, H0599:	l, H0042: 1, H0575: 1,	S0182: 1, S0049: 1, H0596:	1, H0572: 1, H0015: 1,	J0163: 1, S0388: 1, S0051:	1, S6028: 1, H0266: 1,	H0328: 1, H0424: 1, H0032:	1, H0673: 1, S0036: 1,	H0038: 1, H0040: 1, H0551:	1, T0041: 1, S0210: 1,	S0002: 1, H0529: 1, L0763
AR061: AR104: H0427:	AR052:	AR089:	AR053:	AR033:	AKUOI	HOZOH	H0624:	4, HWI	H0615:	2, H005	H0131:	2, H065	S0026: 2	1, H068	S0116:	1, S004	H0497:	1, H004	S0182:	h, H057	1.0163:	1, S6028	H0328:	1, H067	H0038:	1, T004	S0002:]
	Phe-8 to Gly-21.																										
	1637											٠						•									
	995 - 69																										
	232																										
	760494																										
	HSXFL85																										
	222																										

	86-105, 40-56	127-144
1, L0807: 1, L0517: 1, H0520: 1, H0660: 1, H0672: 1, S0328: 1, H0696: 1, L0741: 1, L0742: 1, L0439: 1, L0756: 1, L0780: 1, L0731: 1, S0434: 1, S0196: 1 and H0422: 1.	AR055: 2, AR033: 2, AR060: 2, AR061: 1, AR089: 1, AR096: 1, AR052: 0, AR053: 0, AR039: 0, AR104: 0 S0031: 3, H0624: 1, S6026: 1, S0278: 1, S0222: 1, S0051: 1, H0416: 1, H0644: 1, S0052: 1, S0053: 1, S0028: 1, S0032: 1 and S0260: 1.	AR039: 19, AR053: 9, AR033: 8, AR055: 8, AR096: 7, AR052: 7, AR089: 6, AR060: 6, AR104: 5, AR061: 4 L0740: 8, H0617: 4, L0804: 3, H0068: 2, L0803: 2, H0547: 2, L0747: 2, L0779: 2, H0587: 1, H0581: 1, S0003: 1, H0264: 1, L0649: 1, L0774: 1, L0653:
·		Trp-30 to Ser-36, Lys-54 to Lys-59, Thr-84 to Asn-89.
	1638	1639
	114 - 446	550 550
	233	234
	760510	760822
	223 HNGDQ71 760510	нтол728
	223	224

1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,		01,500	 																						., 0	201	., 10	
HSDZF13 760890 235 532 - 1640 Gly-8 to Ser-14.		91-109, 115-131																										
HSDZF13 760890 235 532 - 1640 Gly-8 to Ser-14.																												
HSDZF13 760890 235 532 - 1640 Gly-8 to Ser-14.			 		-						_																	
HSDZF13 760890 235 532- 1640	1, L0655: 1 and L0362: 1.	1	AR104: 5, AR053: 4,	AR089: 3, AR039: 0	L0777: 5, S0436: 5, S0116:	3, L0805: 3, L0809: 3,	H0696: 3, H0423: 3, S0282:	2, S0354: 2, H0083: 2,	H0316: 2, L0763: 2, L0767:	2, L0776: 2, S0406: 2,	L0779: 2, S0114: 1, H0657:	1, H0656: 1, S0358: 1,	S0444: 1, S0360: 1, H0340:	1, S0046: 1, H0619: 1,	H0455: 1, H0333: 1, H0574:	1, H0559: 1, T0109: 1,	H0156: 1, L0021: 1, T0074:	1, H0318: 1, S0474: 1,	S0049: 1, H0327: 1, H0530:	1, H0615: 1, H0553: 1,	H0673: 1, H0708: 1, H0059:	1, L0065: 1, S0438: 1,	H0207: 1, S0422: 1, L0520:	1, L0769: 1, L0761: 1,	L0521: 1, L0774: 1, L0655:	1, L0659: 1, L0526: 1,	L0793: 1, L0666: 1, L0664:	1, H0659: 1, H0518: 1,
HSDZF13 760890 235 532- 1640		Gly-8 to Ser-14.																										
HSDZF13 760890 235																					·							
HSDZF13 760890		532 - 924												•														
HSDZF13		235																										
225		HSDZF13													-													
		225																		•								

HTOBH39 761762 236 47 - 919 1641 Ala-14 to Arg-19, Val-23 to Pro-38, Ser-44 to Gln-53, Pro-69 to Thr-80. HE9RP73 761860 237 105 - 1642 Val-24 to Gly-35, Sof Gly-48 to Ser-59, Sof-123 to Arg-134.			
HTOBH39 761762 236 47 - 919 1641 Ala-14 to Arg-19, Val-23 to Pro-38, Ser-44 to Gln-53, Pro-69 to Thr-80. HE9RP73 761860 237 105 - 1642 Val-24 to Gly-35, Ser-123 to Arg-134.		87-103	64-82
HTOBH39 761762 236 47 - 919 1641 Ala-14 to Arg-19, Val-23 to Pro-38, Ser-44 to Gln-53, Pro-69 to Thr-80. HE9RP73 761860 237 105 - 1642 Val-24 to Gly-35, Ser-123 to Arg-134.		,	
HTOBH39 761762 236 47 - 919 1641 Ala-14 to Arg-19, Val-23 to Pro-38, Ser-44 to Gln-53, Pro-69 to Thr-80. HE9RP73 761860 237 105 - 1642 Val-24 to Gly-35, Ser-123 to Arg-134.			
HTOBH39 761762 236 47 - 919 1641 Ala-14 to Arg-19, Val-23 to Pro-38, Ser-44 to Gln-53, Pro-69 to Thr-80. HE9RP73 761860 237 105 - 1642 Val-24 to Gly-35, Ser-123 to Arg-134.	L0748: 1, 20362: 2: 1.	19, 13, 11, 8, 3 3 50212: 1, H0042: H0272: 1, 1,	and
HTOBH39 761762 236 47 - 919 1641 Ala-14 to Arg-19, Vai-23 to Pro-38, Ser-44 to Gln-53, Pro-69 to Thr-80. HE9RP73 761860 237 105 - 1642 Vai-24 to Gly-35, Ser-123 to Arg-134.	H0478: 1, 1 1, L0755: 1 L0608: 1, I 1 and S024	21, AR052: 14, AR055: 13, AR033: 9, AR061: 7, AR039: 7, L0439: 7, L0439: 7, L0436: 1, S0430: 1, S0430: 1, S0651: 1 H0634: 1, H0634: 1, H0636: 1, H0666: 1	5, AR053: 1, AR052: 1, AR060: 1, AR096: 0, AR104: 1, H0549: 1
HTOBH39 761762 236 47 - 919 1641 HE9RP73 761860 237 105 - 1642	S0176: 1, 1, 1, 1, 20731: 1, 1, 20026:	AR053: 2 AR096: 1 AR089: 1 AR089: 1 AR060: 4 AR104: 7 L076: 7 L0752: 4, 3, L0748: 50222: 1, 1, 20358: 50214: 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,	AR051: AR055: AR033: AR089: AR039: S0114: 1.
HTOBH39 761762 236 47 - 919 1641 HE9RP73 761860 237 105 - 1642 506		Ala-14 to Arg-19, Val-23 to Pro-38, Ser-44 to Gln-53, Pro-69 to Thr-80.	
HTOBH39 761762 236 47 - 919 HE9RP73 761860 237 105 - 506		1641	1642
HTOBH39 761762			105 - 506
HTOBH39		236	237
HTOBH39		L	761860
		нтовн39	
		226	227

101,0001,10100
37-57
136550, 203310, 269920, 602772
6q14
AR039: 2, AR033: 1, AR089: 1, AR096: 1, AR055: 1, AR060: 0, AR061: 0, AR053: 0 L0759: 6, L0766: 5, H0052: 4, L0770: 4, L0439: 4, L0740: 4, L0747: 4, H0657: 3, S0358: 3, S0003: 3, L0769: 3, L0754: 3, S0376: 2, H0590: 2, H0040:
1644 Leu-60 to Asp-68, Ile-75 to Val-82.
80 - 436
239
764498
Н DРНG57
229

WU	01/90304 PC1/US0	1/104
	126-142	182-199,
	16: 14: 14: 16: 17: 18: 18: 18: 18: 18: 18: 18: 18: 18: 18	
1 and H0506: 1.	AR096: 1, AR055: 1, AR0603: 1, AR060: 1, AR061: 0, AR060: 0, AR039: 0, AR052: 0, AR039: 0, AR052: 0, AR053: 0, AR104: 0 L0748: 10, L0805: 5, L0770: 3, L0777: 3, H0616: 2, S0422: 2, L0777: 3, H0616: 2, L0779: 2, L0777: 3, H0616: 2, L0779: 2, L0777: 2, L0731: 2, L0779: 2, L0772: 2, L0731: 1, H0620: 1, H0631: 1, H0626: 1, H0626: 1, H0620: 1, L0779: 1, L0779	AR096: 18, AR053: 16,
		Asp-3 to Arg-8,
	1645	1646
	267	68°-
	240	241
	765442	766074
	HGBAD15	HOEEP07
	230	231

32.48			-		. =																			- 11.					
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13,	12,	م		<u> </u>	0757:		0776:		0143:		0740:		10657:		0360:		.0109:		10051:	-	H0038:		10560:		.0662:		09990		:0378:
AR052: 13, AR060:			AR033: 8, AR039:	L0748: 11, L0766: 6	.0439: 6, L.0758: 6, L.0757:	, L0794: 4, L0756: 4,	0755: 4, L0805: 3, L0776:	, S0212: 2, S0010: 2,	.0471: 2, S0003: 2, L0143:	1, L0770: 2, L0769: 2,	0803: 2, S0126: 2, L0740:	2, L0759: 2, L0591: 2,	0608: 2, H0685: 1, H0657:	, H0656: 1, H0341: 1,	H0638: 1, S0358: 1, S0360:	1, S0046: 1, S0222: 1,	H0497: 1, H0486: 1, T0109:	, S0474: 1, H0581: 1	H0544: 1, H0009: 1, H0051:	, H0594: 1, H0032: 1	H0674: 1, H0124: 1, H0038:	1, H0616: 1, H0551: 1,	H0488: 1, L0351: 1, H0560.	, S0150: 1, S0422: 1,		, L0809: 1, L0787: 1,	0788: 1, L0789: 1, L0666:	, L0665: 1, H0547: 1,	H0658: 1, H0648: 1, S0378:
Gly-22 to Tyr-30, A	Gly-117 to Val-123, A		_			<u> '</u> 'Ω		<u>.</u>			<u> </u>	Z,		<u>,-î</u>		 1	<u> </u>	<u>-</u>		<u>–</u>	Ē		三		ב	1,	<u> </u>		H
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	102-118	<i>55-77, 75-</i> 91	100-120
			188826, 250100, 250800, 250800
			22913.2- 913.31
1, H0522: 1, S0146: 1, L0747: 1, L0750: 1, L0752: 1, L0731: 1, H0445: 1, L0588: 1, S0026: 1, S0192: 1, S0276: 1 and H0008: 1.	AR096: 2, AR055: 1, AR089: 1, AR060: 1, AR061: 0, AR052: 0, AR053: 0, AR039: 0, AR033: 0, AR104: 0 H0265: 2, L0766: 2, H0656: 1, H0341: 1, H0581: 1, H0634: 1 and S0194: 1.	AR089: 11, AR096: 11, AR060: 7, AR052: 4, AR053: 3, AR033: 3, AR055: 2, AR061: 1, AR104: 1, AR039: 0 H0024: 3, H0622: 3, H0265: 1, S0358: 1, H0486: 1, H0150: 1, H0050: 1, S0316: 1, H0100: 1, H0144: 1, S0328: 1 and L0743: 1.	AR055: 11, AR053: 6, AR060: 6, AR096: 6, AR033: 6, AR061: 6, AR052: 4, AR104: 4, AR089: 4, AR039: 3 H0424: 16, S0380: 13,
	Met-1 to Arg-6.	Ser-42 to Arg-47, Thr-115 to Ser-127, Ser-130 to Trp-136.	Asp-9 to Ile-22, Ser-64 to Leu-69, Thr-91 to Ser-100, Lys-162 to Gln-172.
	1647	1648	1649
	19 - 378	905 - 1387	299 - 832
	242	243	244
	766558	766868	767356
	нгінтѕо	HANGD38	234 HPMGQ75 767356
	232	233	234

VO 01/	90304	<u> </u>]	PC'	r/U	S01	/16	450
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L0755	10545		9410	•	0751:		0378:		0376:	<u>۔</u>	0776:		0599:	~ .	10638:	~ ~	10617	_	.0768:		0528:	_	H0670		0439.		30218:
750: 12 44: 9,	192: 9 3: 8: 1	747:8	0:7,S	752: 7	4: 6, L	7423: 6	72: 5, 8	759:5	i6: 4, S	0150:4	5: 4, L	328: 4	4: 4, I	0685:	3:3, F	3318: 3	97:3,1	144:3	77: 3, I	774: 3	3: 3, I	126:3	58: 3, 1	3696: 3	2: 3, I	757:3	19: 2,
3, L07 0, S04	3, 9, S0	8; 8; C	, S036	: 7, LO	5, S037	i. 6, H(, H067	: 5, 1.0	4, S035	5. 4, H	,1077	: 4, S0	, SO43	2: 4, H	, H048	5: 3, H(3, H05	t: 3, SC	, 1.076	1:3,10	1, 1.078	3, SC	3, H06	: 3, HC	,1074	:3,10	3, H01
L0748: 13, L0750: 12, S0440: 10, S0444: 9, L0755:	9, L0758: 9, S0192: 9, H0484: 8, S0358: 8, H0545:	8, L0809: 8, L0747: 8,	.0749: 8, S0360: 7, S0410:	, S0406: 7, L0752: 7	.0766: 6, S0374: 6, L0751:	6, L0754: 6, H0423: 6,	S0442: 5, H0672: 5, S0378:	, S0404: 5, L0759: 5,	H0556: 4, S0356: 4, S0376:	4, H0546: 4, H0150: 4,	S0438: 4, L0775: 4, L07	4, L0518: 4, S0328: 4,	.0740: 4, S0434: 4, L0599:	4, H0422: 4, H0685: 3,	S0116: 3, H0483: 3, H0638:	1, H0486: 3, H0318: 3,	H0309: 3, H0597: 3, H0617:	, H0494: 3, S0144: 3,	.0771: 3, L0767: 3, L0768:	3, L0794: 3, L0774: 3	.0806: 3, L.0783: 3, L.0528:	i, H0593: 3, S0126: 3,	H0690: 3, H0658: 3, H0670:	3, S0330: 3, H0696: 3,	S0028: 3, L0742: 3, L0439:	3, L0731: 3, L0757: 3,	H0543: 3, H0149: 2, S0218:
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VO 01/90304	PCT/US01/16450
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2, H0341: 2, H0306: 2, H0402: 2, S0420: 2, H0402: 2, S0420: 2, H0392: 2, H0333: 2, H0101: 2, H0323: 2, H0024: 2, H0644: 2, H0616: 2, H0649: 2, L0657: 2, L0659: 2, H0648: 2, H0648: 2, H0659: 2, H0648: 2, H0659: 2, H0648: 2, L0651: 2, S0392: 2, L0743: 2, S0392: 2, L0743: 2, S0396: 2, H0542: 2, H0542: 2, H0542: 1, H0171: 1, H0170: 1, H0171: 1, H0170: 1, H0171: 1, H0294: 1, S0114: 1,	H0657: 1, H0656: 1, L 1, S0212: 1, H0255: 1, H0663: 1, S0418: 1, S1, H0676: 1, S0408: 1, F0008: 1, H0637: 1, H 1, H0393: 1, S0278: 1, H0369: 1, S0222: 1, H
2, H040231: H040231: H040231: H040231: H040231: H04231: H00231: H00231: H00231: H00231: H00231: H00548: H00548: H00540: H00540	H0657: 1, S021 H0663: 1, H067 T0008: 1, H035 H0369:
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1622:		575:	A74.	<u> </u>)123:		010:)687:)06: 		032:		[63:		264:		131:		L0762:		772:		562:		379:
100372. 1, 1574: 1, LO	H0427: 1,	156: 1, HU	HUZ/4: 1,	H0596: 1,	1086: 1, HC	H0012: 1,	057: 1, TO	H0594: 1,	188: 1, HC	H0252: 1,	368: 1, TO	H0213: 1,	055: 1, H0	H0674: 1,	36: 1, HO	H0634: 1,	067: 1, HO	H0625: 1,	466: 1, H0	10633: 1,	529: 1, LO	.0770: 1,	761: 1, LO	.0646: 1,	321: 1, LOC	.5564: 1,	555: 1, LO
1, n0550: 1, n0522: 1, H0586: 1, H0574: 1, L0622:	l, H0013: 1, H0427: 1,	S0280: 1, H0156: 1, H0575:	I, H0004: I, H0274: I, H023: 1 T0048: 1 S0474:	, H0085: 1, H0596: 1,	H0544: 1, H0086: 1, H0123:	I, L0471: 1, H0012: 1,	620: 1, H0	1, H0375: 1, H0594: 1,	H0179: 1, H0188: 1, H0687:	, Н0284: 1, Н0252: 1	F0023: 1, S0368: 1, T0006:	, H0604: 1, H0213: 1,	H0553: 1, L0055: 1, H0032:	, H0673: 1, H0674: 1	S0366: 1, S0036: 1, H0163:	, H0038: 1, H0634: 1,	H0087: 1, T0067: 1, H0264:	, T0041: 1, H0625: 1	H0561: 1, S0466: 1, H0131:	l, S0150: 1, H0633: 1,	472: 1, HO	1, L0763: 1, L0770: 1	3905: 1, L0761: 1, L0772:	.0372: 1, I	L0374: 1, L0521: 1, L0662:	.0364: 1, I	.0378: 1, L0655: 1, L0379:
<u>: E</u>	[, <u>1</u>	<u>5</u>	1,1 11,1	1,1	H	1,1	丑	<u></u>	H H	<u></u>	2	<u></u>	丑	<u></u>	<u>80</u>	1,1	紐	<u> </u>	R	<u>, , , , , , , , , , , , , , , , , , , </u>	<u>Š</u>	1,1	<u> </u>	1, I	<u>3</u>	1,1	Ì
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	56-72
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4. 30 ES 52 52 52	
1, L0656: 1, L0659: 1, 1, L0540: 1, L0526: 1, L0384: 1, L0548: 1, L0541: 1, 1, L0664: 1, L0665: 1, 1, L0664: 1, L0665: 1, 1, H0651: 1, H0547: 1, H0683: 1, H0651: 1, H0539: 1, H0518: 1, S0350: 1, H0555: 1, H0576: 1, H0627: 1, S3014: 1, S0027: 1, S0032: 1, L0756: 1, L0786: 1, L0777: 1, L0753: 1, H0445: 1, L0591: 1, L0592: 1,	AR052: 56, AR053: 51, AR052: 56, AR053: 51, AR056: 43, AR089: 39, AR055: 39, AR033: 34, AR104: 21, AR039: 17 H0575: 138, L0599: 44, H0642: 13, H0024: 13, H0652: 11, H0123: 9, H0647: 9, L0776: 8, H0375: 5, L0806: 5, L0653: 5, H0649: 4, L0776: 4, H0427: 3, H0646: 3, H0208: 2, H0050: 2, T0003: 2, L0600: 2, H0586: 1, H0318: 1, H0059: 1, S0472: 1, L0378: 1, S0296: 1, H0593: 1,
1, 10540: 10540: 1, 10540: 1, 1066: 1, 1066: 1, 1066: 1, 1056: 1, 1057: 1, 1059: 1, 1059: 1, 1059:	AR052: AR061: AR104: H0672: H0647: 5, L080 5, L080 1, H068
	1650 Tyr-15 to Cys-22.
	1650
	285 - 695
	245
·	767674
	нВЛН66 7674
	235

	01/30004	101/000110
	32-55	44-92, 1- 24, 76-92, 41-57
		·
H0539: 1 and L0589: 1.	AR033: 8, AR055: 7, AR052: 5, AR053: 4, AR061: 4, AR060: 4, AR089: 4, AR096: 3, AR104: 3, AR039: 0 L0731: 5, L0758: 5, H0620: 3, L0766: 3, S0360: 2, S0002: 2, L0809: 2, L0791: 2, L0748: 2, L0439: 2, L0747: 2, L0601: 2, H0556: 1, S0282: 1, H0125: 1, T0114: 1, H0581: 1, H0550: 1, S0222: 1, H0592: 1, L0769: 1, L076: 1, L0774: 1, L076: 1, L0774: 1, L0776: 1, L0773: 1, L0543: 1, H0670: 1, H0555: 1, L0776: 1, L0776: 1, L0778: 1, L0543: 1, H0670: 1, H0555: 1, S0260: 1, L0757: 1, S0260: 1, L0596: 1 and L0361: 1.	AR039: 2, AR096: 2, AR055: 2, AR104: 1, AR033: 1, AR061: 1, AR089: 0, AR053: 0,
	Lys-17 to Cys-29, Thr-69 to Cys-79, Arg-92 to Gly-99.	
	1651	1652
	1022 - 672	26 - 361
	246	247
	768346	768776
	HEGBB78	HAJBC01
	236	237

	/9030	<u> </u>																					<u> </u>	.,0	301	1/10	
	119-137																										
	118425,	118425,	142335,	152427,	163729,	176450,	180105,	190605,	276000,	276000,	600510,	600725				<u> </u>		-		-			*****			•	
	7q35-q36																										
AR060: 0, AR052: 0 H0561: 1	Gly-140 to Glu-149. AR055: 8, AR060: 6,			AR039: 3, AR053: 3	L0731: 17, L0439: 9,	H0056: 8, L0438: 6, L0759:	6, L0157: 4, H0644: 4,	S0010: 3, L0774: 3, L0747:	3, S0346: 2, H0309: 2,	S0003: 2, S0002: 2, L0646:	2, L0803: 2, L0804: 2,	H0539: 2, S0406: 2, L0748:	2, L0754: 2, L0745: 2,	L0779: 2, L0777: 2, L0780:	2, L0752: 2, H0556: 1,	T0049: 1, H0580: 1, S0045:	1, S0300: 1, H0411: 1,	S0222: 1, H0391: 1, H0333:	1, S0474: 1, L0109: 1,	H0196: 1, H0596: 1, H0050:	1, L0471: 1, H0014: 1,	H0373: 1, H0020: 1, S0051:	1, H0687: 1, L0483: 1,	H0553: 1, H0674: 1, H0163:	1, H0038: 1, H0059: 1,	H0625: 1, H0561: 1, S0144:	1, H0538: 1, S0426: 1,
	1653 Gly-14																										
	248 25 - 471	-																									
	769003 2		-	· · · · · ·					•				•								••••			···-	<u> </u>		
	HHGCP75														_												
	238																										

	252-269, 219-235, 121-137
L0770: 1, L0769: 1, L0764: 1, L0766: 1, L0809: 1, L0791: 1, L0792: 1, H0519: 1, H0521: 1, S0028: 1, L0751: 1, L0749: 1, L0750: 1, L0755: 1, H0668: 1, H0136: 1, H0423: 1 and H0422: 1.	AR055: 20, AR033: 12, AR050: 11, AR052: 11, AR060: 10, AR089: 10, AR061: 9, AR089: 10, AR104: 3, AR039: 3, L0766: 11, L0769: 3, L0761: 3, L0655: 3, L0777: 3, L0780: 3, H0543: 3, H0556: 2, S0476: 2, H0039: 2, L0794: 2, L0804: 2, L0805: 2, L0787: 2, L0747: 2, L0362: 2, S0026: 2, H0542: 2, L0005: 1, S0356: 1, S0360: 1, H0580: 1, S0132: 1, H0538: 1, L0483: 1, L0646: 1, L0771: 1, L5574: 1, L0388: 1, L0653: 1, L0606: 1, L0388: 1, L0653: 1, L0606: 1, L0388: 1, L0436: 1, L0749: 1 and S0194: 1.
	Pro-17 to Trp-26, Pro-76 to Arg-81, Asp-99 to Gly-106, Pro-148 to His-157, Glu-178 to Glu-185, Leu-195 to Pro-201. I
	1654
·	24- 1031
	249
	771350
	HAID095
	239

3, AR061: 2, 8q21 124080, 2, AR060: 1, 1, AR052: 1, 202010, 0, AR089: 0, 602476, 0, AR089: 0, 602476, 0, AR089: 0, 602476, 0, AR089: 3, L0744: 602667 4, L0803: 3, L0744: 602667 4, L0803: 3, L0744: 602667 5, L0663: 4, 602667 5, L0663: 4, 602667 6: 1, L0766: 2, 2, H0686: 1, S0040: 6: 1, H0621: 1, 1, H0021: 1, 1, H0021: 1, L0769: 2, L076		
250 19 - 759 1655 Lys-20 to Tyr-27, AR096: 3, AR061: 2, Bq21 Tyr-35 to Ser-49. AR033: 2, AR061: 2, Bq21 AR055: 0, AR089: 0, AR099: 3, L0748: 3, L0772: 4, L0803: 3, L0748: 3, L0772: 4, L0803: 3, L0748: 2, L0749: 2, L0779: 2, L0756: 2, L0749: 1, H0650: 1, H0669: 1, H0669: 1, H0669: 1, H0669: 1, H0669: 1, H0669: 1, L0809: 1, L0768: 1, L0809: 1, L0664: 1, L0809: 1, L0664: 1, L0669: 1, H0659: 1, H0669: 1, H0659: 1, H0669: 1,	132-150, 78-94	36-65
250 19 - 759 1655 Lys-20 to Tyr-27, AR096: 3, AR061: 2, AR033: 2, AR060: 1, AR053: 1, AR052: 1, AR055: 0, AR089: 0, AR104: 0 S044: 5, L0663: 4, L0748: 2, L0748: 3, L0777: 4, L0803: 3, L0748: 3, L0777: 4, L0803: 3, L0749: 3, L0777: 4, L0803: 3, L0749: 2, L0778: 2, L0778: 2, L0778: 2, L0776: 2, L0778: 2, L0778: 2, L0776: 1, L0021: 1, H0650: 1, H0650: 1, H0059: 1, H0059: 1, H0059: 1, L0764: 1, L0769: 2, Ser-64 to Lys-84, AR061: 6, AR033: 6, AR089: 5, AR104: 4, L0766: 3, S0358: 2, S0278:	124080, 202010, 202010, 214400, 602476,	
250 19 - 759 1655 Lys-20 to Tyr-27, Tyr-35 to Ser-49.	8921	**
250 19-759	AR096: 3, AR061: 2, AR053: 2, AR060: 1, AR053: 1, AR052: 1, AR055: 1, AR055: 0, AR089: 0, AR104: 0 S0414: 5, L0663: 4, L0777: 4, L0803: 3, L0744: 3, L0752: 3, L0731: 3, L0758: 2, L0743: 2, L0758: 2, L0749: 2, L0758: 2, L0749: 2, L0758: 2, H0666: 1, S0040: 1, H0650: 1, H0013: 1, L0021 1, S0346: 1, H0663: 1, H0687: 1, H0648: 1, H0687: 1, L0764: 1, L0664: 1, L0665: 1, L0664: 1, L0665: 1, L0664: 1, L0665: 1, L0759: 1, R0521: 1, H06522: 1, L0759: 1, S0031: 1, H06522: 1, L0759: 1, S0031: 1, H0654: 1, L0665: 1, H0659: 1, H0669:	AR096: 17, AR055: 9, AR060: 8, AR039: 7, AR061: 6, AR033: 6, AR052: 6, AR053: 5, AR089: 5, AR104: 4 L0766: 3, S0358: 2, S0278
250 19-759	Lys-20 to Tyr-27, Tyr-35 to Ser-49.	Met-1 to Gly-16, Ser-32 to Lys-38, Ser-64 to Lys-84.
250	1655	1656
	19 - 759	79 - 432
240 HE8UD19 771648 241 HMAIT58 771900		251
240 HE8UD19 241 HMAIT58		771900
240	HE8UD19	HMAIT58
	240	241

	402.418	71-89, 19-	28-58
2, L0775: 2, L0756: 2, H0650: 1, H0656: 1, H0402: 1, H0013: 1, S0049: 1, H0644: 1, H0652: 1, S0142: 1, S0002: 1, L0770: 1, L0768: 1, L0649: 1, L0784: 1, L0776: 1, H0521: 1, H0522: 1 and H0555: 1.	AR055: 1, AR052: 1, AR053: 1, AR061: 1, AR089: 1, AR033: 1, AR104: 1, AR060: 1, AR096: 0, AR039: 0 L0439: 4, H0013: 2, H0497: 1, T0010: 1, T0041: 1, H0144: 1 and L0438: 1.	AR096: 8, AR089: 6, AR052: 5, AR053: 5, AR039: 4, AR033: 3, AR060: 2, AR104: 2, AR055: 2, AR061: 1 L0750: 4, H0265: 3, L0794: 3, L0731: 3, H0635: 2, H0494: 2, L0766: 2, S0116: 1, H0052: 1, H0264: 1, S0002: 1, L0769: 1, L0764: 1, L0768: 1, H0144: 1, L0608: 1 and L0601: 1.	AR052: 2, AR053: 2,
			1659 Leu-19 to Asn-29,
	1657	1658	1659
	104 - 1435	423	983 -
	252	253	254
	712277	772639	772840
	242 HDAAE77 772217	243 HKAOJ07 772639	HDTFC73
	242	243	244

WO 01/90304	PCT/US01/16450
	44-60, 129-145
	<u> </u>
AR096: 1, AR089: 1, AR055: 1, AR104: 1, AR061: 1, AR033: 1, AR060: 1 L0439: 7, L0777: 3, S0007: 2, H0031: 2, L0438: 2, L0411: 1, H0662: 1, H0638: 1, S0222: 1, H0486: 1, L0021: 1, H0052: 1, T0010: 1, H0032: 1, H0268: 1, L0351: 1, L0766: 1, L0804: 1, L0655: 1, L0809: 1, S0216: 1 and H0522: 1.	AR096: 2, AR089: 2, AR104: 1, AR060: 1, AR052: 1, AR033: 0, AR039: 0, AR061: 0 S0476: 11, H0556: 10, H0265: 4, H0635: 4, H0657: 2, H0638: 2, S0132: 2, H0036: 2, L0601: 2, H0423: 2, H0713: 1, S0134: 1, S0298: 1, H0486: 1, H0069: 1, H0575: 1, T0082: 1, H0581: 1, L0471: 1, H0321: 1, H0591: 1, H0560: 1, H0641: 1, L0506: 1, L0775: 1, L0657: 1, H0435: 1, H0518: 1, H0521: 1, S0406: 1, L0749: 1 and H0543: 1.
Glu-96 to Lys-101.	Pro-13 to Ser-18.
	1660
1303	74 - 538
	255
	773040
	HDTF132
	245

	301/1043
48-64, 72- 88	
4 89	
,	
45, 33, 21, 19, 19, 19, 3, 80358: 2, H0624: 1, 1, 1, H0574: 1, H0598: 1, H0598: 1, H0598: 1, H0598:	l, C0497: I,
46, AR055: 34, AR052: 26, AR061: 21, AR104: 9, L0751: 6, 1, L0752: 5, 1; 4, L0761: 3, 1, H0657: 2, 2, L0772: 2, L0778: 2, L0766: 2, 1; 1, H0295: 1, H0661: 1, S, H0642: 1, H0545: 1, H0642: 1, H0660: 1, S0144: 1, L0560: 1, S0144: 1, L056	, L0646: .0499: 1,] , L0783:
AR033: 46, AR055: 45, AR039: 38, AR053: 35, AR089: 34, AR052: 33, AR096: 26, AR061: 21, AR060: 21, AR104: 19 H0617: 9, L0751: 6, L0750: 5, L0752: 5, L0770: 4, L0747: 4, L0761: 3, L0775: 3, H0657: 2, S0358: 2, S0444: 2, H0457: 2, L0764: 2, L0772: 2, L0764: 2, L0766: 2, L0774: 2, L0742: 2, L0748: 2, L0757: 2, L0758: 2, H0624: 1, H0685: 1, H0295: 1, S0114: 1, H0661: 1, S0140: 1, H0013: 1, H0243: 1, H0549: 1, H0547: 1, H0549: 1, H0543: 1, H0549: 1, H0543: 1, H0549: 1, H0543: 1, H0616: 1, H0412: 1, H0598: 1, H0135: 1, H0163: 1, H0616: 1, H0412: 1, H0599: 1, H0494: 1, L5565:	1, L0373; 1, L0646; 1, L0768: 1, L0499: 1, L0497; 1, L0513: 1, L0783: 1,
1661 Gly-5 to Gln-12, Lys-98 to Pro-106.	
1661	
256 47 - 373	
526	
773347	
246 HLQCY70 773347	

WO 01/90304		PCT/US01/16
	61-77	144-160, 99-115
		·
L0384: 1, L0519: 1, L3872: 1, L0368: 1, L0665: 1, S0053: 1, H0144: 1, H0670: 1, H0672: 1, H0651: 1, H0696: 1, S0406: 1, L0740: 1, L0754: 1, L0780: 1, L0731: 1, L0596: 1, S0026: 1, H0543: 1, H0677: 1 and H0352: 1.	AR055: 5, AR052: 3, AR061: 3, AR033: 3, AR060: 2, AR089: 2, AR039: 2, AR104: 2, AR053: 1, AR096: 1 S0045: 1, S0222: 1, H0250: 1, H0617: 1 and S0028: 1.	AR033: 13, AR104: 10, AR055: 7, AR060: 5, AR061: 5, AR052: 5, AR096: 4, AR089: 4, AR053: 3, AR039: 2 S0010: 4, S0222: 3, H0455: 2, L0803: 2, L0439: 2, L0745: 2, S0282: 1, S0400: 1, H0722: 1, H0456: 1, H0441: 1, S0346: 1, H0714: 1, H0509: 1, L0769:
	1662 Lys-31 to Lys-39, Gln-41 to Lys-46, Pro-79 to Ala-85, Glu-95 to Leu-100.	
	1662	
	2 - 301	649 - 41
	257	258
	773740	774276
·	HELDG78	HAGEK19
	247	248

WO 01/90304			FC1/0	SU1/104
114-130, 147-163		60-78, 17- 33	90-116, 51-70, 79- 95, 21-37	44-65, 92- 112, 21-
L0756: 1, S0434: 1 and S0106: 1. AR055: 11, AR033: 9, AR060: 6, AR104: 6, AR096: 6, AR061: 5, AR089: 4, AR053: 4.	AR052: 4, AR039: 3 L0740: 2, S0222: 1, T0082: 1, T0110: 1, T0010: 1, L0483: 1, L0763: 1, L0639: 1, L0747: 1, L0777: 1, L0758: 1 and L0599: 1.	AR052: 8, AR053: 7, AR033: 3, AR055: 3, AR096: 3, AR089: 2, AR061: 2, AR060: 2, AR104: 1, AR039: 0 L0777: 5, L0439: 2, L0596: 2, T0004: 1, L0658: 1, H0518: 1, H0521: 1, L0731: 1 and S0106: 1.	AR055: 17, AR033: 13, AR039: 12, AR052: 10, AR089: 10, AR053: 10, AR061: 9, AR060: 8, AR096: 7, AR104: 7 H0063: 1	AR055: 2, AR089: 1, AR104: 1, AR060: 1,
Asp-20 to Leu-26, Gln-55 to Thr-60, Asn-74 to Asn-86.			Met-1 to Arg-7.	1667 Gln-11 to Arg-21.
1664		1665	1666	1667
291 - 854		465 - 764	273 - 734	152 - 592
259		260	261	262
774569	•	774739	775247	775419
H2CBA34		250 HDPTC79	HTHBY73	HE8DL19
249		250	251	252

· · · · · · · · · · · · · · · · · · ·	
37, 124- 140	102-131
	266: 754: 575: 662: 7713: 0004: 0641:
AR096: 0, AR061: 0, AR033: 0, AR053: 0, AR039: 0, AR052: 0 H0013: 1, S0214: 1, H0615: 1 and L0544: 1.	AR055: 7, AR052: 5, AR096: 5, AR060: 4, AR096: 5, AR060: 4, AR089: 3, AR104: 3, AR061: 3, AR104: 3, AR061: 3, AR039: 2 L0766: 8, L0777: 7, L0794: 5, L0770: 4, H0266: 3, L0803: 3, L0776: 3, H0144: 3, L0740: 3, L0754: 3, L0750: 3, S0222: 2, S0414: 2, H0013: 2, H0575: 2, H0590: 2, L0764: 2, L0662: 2, L0809: 2, L0764: 2, L0662: 2, L0809: 2, L0769: 2, H0556: 1, H0641: 1, H0556: 1, H0641: 1, H0497: 1, L0021: 1, H0641: 1, H0497: 1, H0598: 1, H0591: 1, H0412: 1, H0598: 1, H0591: 1, H0412: 1, H0560: 1, H0641: 1, L0771: 1, L0804: 1, L0775:
AR096: AR033: AR039: H0013: H0615: 1	AR055: AR056: AR056: L0796: L0794: 5 3, L0803 H0144: 3 3, L0750 2, H0590 L0769: 2 2, L0809 H0696: 2 2, S0026 H0556: 1 1, S0045: H0697: 1 1, H0598 H0412: 1 1, L0796
	Leu-12 to Thr-19, Arg-25 to Glu-39, Glu-41 to Cys-48, Ser-65 to Ser-71, Pro-84 to Gly-89, Ser-97 to Arg-103.
	1668
	31 - 423
	563
	775455
	HMEGE46
	253

VO 01/90304	PC1/0501/10450
•	349-366, 272-288, 380-396
6: 1, 1, L0788: 20: 1, 1, H0522: 55: 1, 1, S0031: 33: 1, 1 and	22: 6, 33: 4, 36: 3, 36: 3, 37: 11, 37: 2, 37: 2
1, L0375: 1, L0806: 1, L0805: 1, L0659: 1, L0788: 1, L0666: 1, H0520: 1, H0660: 1, H0521: 1, H0522: 1, S0406: 1, H0555: 1, S0028: 1, L0747: 1, S0031: 1, L0608: 1, L0593: 1, H0668: 1, S0242: 1 and H0423: 1.	AR055: 6, AR052: 6, AR053: 4, AR060: 4, AR089: 4, AR060: 3, AR096: 3, AR104: 2, AR039: 2 L0748: 11, L0758: 11, L0758: 11, L0594: 6, L0439: 5, L0759: 5, H0556: 4, L0769: 4, S0442: 3, H0100: 3, L0662: 3, L0666: 3, L076: 2, L076: 2, L0770: 2, L0649: 2, L0770: 2, L0649: 2, L0653: 2, L0770: 2, L0669: 2, L0653: 2, L0770: 2, L0669: 2, L0653: 2, L0770: 2, L0669: 2, L0653: 2, L0770: 2, L0569: 2, L0777: 2, L0740: 2, L0757: 2, L0740: 2, L0757: 2, L0758: 2, L0757: 2, L0758: 2, L0559: 2, L0559
	Val-29 to Asp-34, Gln-78 to Gln-86, Val-94 to Leu-100, Glu-112 to Leu-117, Gln-119 to Ile-133, Glu-152 to Ala-157, Thr-159 to Gln-168, Lys-209 to Glu-218, 5 Thr-225 to Ser-231, Trp-410 to Trp-415, Ala-505 to Ser-510. In-205 to Ser-510.
	1669
·	125 - 1657
	764
	778081
	HTEIA85
	254

VO 01/90304	PCT/US01/16450
108-134, 42-58	52-72, 7- 23
AR053: 14, AR033: 12, AR060: 10, AR089: 8, AR096: 7, AR061: 7, AR104: 5, AR039: 4 H0046: 6, L0758: 5, L0794: 3, L0779: 3, H0052: 2, H0424: 2, H0052: 2, H0424: 2, H0052: 2, L0751: 2, H0690: 2, S3014: 2, L0743: 2, L0751: 2, L0731: 2, H0295: 1, S0001: 1, S0360: 1, S0278: 1, S0002: 1, H0457: 1, H0031: 1, L0764: 1, L0773: 1, L0764: 1, L0773: 1, L0659: 1, L0664: 1, L0665: 1, H0547: 1, H0435: 1, H0670: 1, L0664: 1, L0748: 1, L0599: 1, L0661: 1, L0748: 1, L0599: 1, L0761: 1, H0435: 1, H0670: 1, L0664: 1, L0768: 1, L0769: 1, L0768: 1, L0768: 1, L0769: 1, L0768: 1, L0768: 1, L0769: 1, L0768: 1, L0768: 1, L0769: 1, L0778: 1, L077	AR053: 1, AR060: 1, AR055: 1, AR033: 1, AR061: 0, AR089: 0, AR039: 0, AR104: 0 L0758: 13, L0756: 3, L0752: 3, L0438: 2, H0176:
	1671 Lys-31 to Thr-39.
	1671
707	539 - 240
	266
	778291
	256 HLYCQ80
	256

	91-107	103-120
1, H0261: 1, H0309: 1, H0081: 1, H0029: 1, H0038: 1, H0616: 1, H0202: 1, L0369: 1, L0766: 1, L0774: 1, L0776: 1, L0635: 1, L0809: 1, L0791: 1, H0547: 1, H0711: 1, H0690: 1, S0152: 1, H0479: 1, L0743: 1, L0439: 1, L0750: 1, L0777: 1, L0755: 1, H0445: 1 and L0588: 1.	AR055: 13, AR060: 9, AR052: 9, AR061: 8, AR053: 8, AR033: 5, AR089: 4, AR096: 3, AR104: 2, AR039: 0 L0761: 3, L0439: 3, L0747: 3, L0766: 2, H0659: 2, L0779: 2, L0777: 2, H0170: 1, S0360: 1, H0550: 1, H0023: 1, H0018: 1, H0641: 1, L0763: 1, L0769: L0774: 1, L0803: 1, L0774: 1, L0655: 1, L0666:	ARO52: 285, AR089: 170, ARO96: 161, AR053: 143, AR060: 83, AR104: 64, AR033: 49, AR039: 43,
	1672 Met-1 to Gln-8, Leu-17 to Leu-29, Gln-109 to Thr-115.	Glu-53 to Asp-58, Trp-98 to Lys-103, Leu-131 to Arg-144.
	1672	1673
	162 - 611	52 - 630
		268
	778504	779291
	HE2OF81	HTEBB88
	257	258

WO 01/90:	304																				P	CI	/U	S01	/16	450
	18-44, 75-	3																								
	121011,	129500,	253700,	601885,	602221																					
	13q12				•																					
AR061: 42, AR055: 40 L0758: 6, H0616: 3, H0038: 2 and H0618: 1.	AR039: 23, AR104: 18, AR033: 17 AR096: 10	AR052: 8, AR053: 7,		AR060: 5, AR061: 4	L0754: 16, H0617: 8,	S0360: 6, H0551: 6, L0748:	6, L0750: 6, H0543: 6,	L0766: 5, L0666: 5, L0751:	5, L0747: 5, S0418: 4,	H0553: 4, L0665: 4, H0542:	4, H0586: 3, S0414: 3,	H0264: 3, H0494: 3, S0344:	3, L0769: 3, L0438: 3,	H0547: 3, H0519: 3, H0521:	3, L0740: 3, L0757: 3,	S0192: 3, H0656: 2, H0254:	2, H0255: 2, S0046: 2,	S0132: 2, H0587: 2, H0559:	2, H0618: 2, H0620: 2,	H0199: 2, H0688: 2, L0770:	2, L0372: 2, L0642: 2,	L0771: 2, L0662: 2, L0653:	2, L0659: 2, L0783: 2,	H0435: 2, H0660: 2, L0602:	2, H0436: 2, S3014: 2,	L0731: 2, L0759: 2, L0588:
	Asn-14 to Ser-19, Asn-46 to Phe-51	17,																								
	1674	-			•		-													•					,	
	81 - 461											•								•		•				
	569																									
	119607																									
	HWHGD8	1				٠																				
	259																									

WO 01/90304	PCT/US01/1645
2, H0265: 1, S0110: 1, S0356: 1, H0632: 11, H0597: 11, H0428: 1, H0428: 1, H0428:	
L0601: 3 (0352: 2, H0583: 2, H0583: 2, H0583: 1, H0662: 1, S0444: 1, S0444: 1, S0447: 1, H0599: 1, H0594: 1, H0594: 1, H0181: 3564: 1, B0663: 1, S0448: 1, S0488: 1, S0448: 1, S0448: 1, S0488: 1, S0488: 1, S0448: 1, S0488: 1, S	131:1,1 10763: 10646:1,1 10646:1,1 10649:1 10607:1,1 10607:1,1
2, L0599: 2, L0601: 2, H0506: 2, H0352: 2, H0265: 1, H0556: 1, H0583: 1, H0657: 1, H0341: 1, S0110: 1, H0484: 1, H0662: 1, H0402: 1, S0420: 1, S0356: 1, S0354: 1, S0444: 1, S0300: 1, L0717: 1, S0278: 1, H0415: 1, H0497: 1, H0632: 1, H00486: 1, H0599: 1, H0179: 1, H0594: 1, H0179: 1, H0271: 1, H0428: 1, H0642: 1, H0181: 1, L0055: 1, S0364: 1, H0040: 1, H0634: 1, H0663: 1, H0488: 1, H06413: 1, H0100:	1, 10501; 1, 50749; 1, 50440; 1, 50440; 1, H0529; 1, L0763; 1, L0763; 1, L0763; 1, L0772; 1, L0646; 1, L0800; 1, L0644; 1, L0773; 1, L0521; 1, L0649; 1, L0381; 1, L0375; 1, L0651; 1, L0657; 1, L0657; 1, L0657; 1, L0677; 1, L0677; 1, L0677; 1, L0807; 1, L08
1, 5 1, 5 1, 5 1, 5 1, 5 1, 5 1, 5 1, 5	11. 12. 12. 12. 13. 13. 13. 13. 13. 13. 13. 13. 13. 13
· .	

WO 01/90304	PC1/0501/16450
	102-119
1, L0663: 1, S0428: 1, H0144: 1, H0593: 1, S0126: 1, H0690: 1, H0670: 1, S0328: 1, S0380: 1, S0350: 1, H0522: 1, S0188: 1, S0027: 1, S0206: 1, L0744: 1, L0439: 1, L0756: 1, L0777: 1, L0755: 1, H0445: 1, H0136: 1, S0042: 1 and L0697: 1.	AR052: 5, AR053: 3, AR096: 3, AR033: 3, AR089: 2, AR060: 2, AR104: 2, AR061: 1, AR055: 0, AR039: 0 L0439: 7, L0759: 5, H0624: 4, H0170: 4, S0003: 4, L0766: 4, H0657: 3, H0013: 3, L0438: 3, H0068: 2, L0598: 2, L0646: 2, L0794: 2, L0659: 2, L0647: 2, L0666: 2, H0520: 2, L0747: 2, L0756: 2, L0779: 2, L0777: 2, L0588: 2, L0592: 2, H0171: 1, H0556: 1, S0376: 1, S0045: 1, S0222: 1, H0586: 1, T0114: 1, H0581: 1, L0471: 1, H0355: 1, S6028: 1, S0214: 1, H0615: 1, H0428: 1,
	Glu-37 to Asn-44.
	1675
	143 - 628
	270
	779663
	н w АDH6 7
	260 1

WO 01/90304			270501710-
	86-110, 7- 32, 65-82	99-121, 124-140	60-77, 22- 38
·			
	·	****	
H0039: 1, H0591: 1, H0040: 1, T0004: 1, L0763: 1, L0768: 1, L0774: 1, L0806: 1, L065: 1, L0352: 1, H0519: 1, H0690: 1, H0648: 1, H0518: 1, H0518: 1, H0518: 1, L0753: 1, L0758: 1, L0758: 1, L0731: 1, L0758: 1, L0599: 1, L0599: 1, L0593: 1, S0026: 1, H0667: 1 and H0543: 1.	AR052: 3, AR033: 2, AR104: 2, AR089: 2, AR055: 2, AR039: 2, AR096: 2, AR053: 2, AR061: 1, AR060: 1 L0766: 5, H0494: 2, L0755: 2, L0800: 1, L0773: 1 and L0777: 1.	AR052: 3, AR053: 2, AR104: 2, AR089: 1, AR033: 1, AR061: 1, AR060: 1, AR096: 1, AR055: 0, AR039: 0 H0543: 1	AR033: 20, AR104: 16, AR055: 8, AR061: 7, AR060: 5, AR053: 5,
	1676 Asn-3 to Phe-9.	1677 Met-1 to Glu-10.	Pro-89 to Phe-96.
	1676	1677	1678
	138 - 530	29 - 457	822 - 502
	271	272	273
	779838	780458	780804
·	HKADC82	HHESK83	HMIAT16
	261	262	263

WO 01/90304		PCT/US01	/164
	9-29, 120- 136	77-95, 10- 26	80-102, 1-
439: D6:		16: 10: 43: 1.	
AR052: 5, AR089: 5, AR096: 4, AR039: 3 S0414: 3, S0036: 3, L0439: 3, H0327: 2, H0051: 2, S6028: 2, S0282: 1, H0406: 1, H0438: 1, S0010: 1, S0038: 1, S0260: 1 and S0412: 1.	AR053: 2, AR096: 1, AR089: 1, AR060: 1, AR104: 1, AR055: 1, AR033: 0, AR039: 0, AR061: 0, AR052: 0 H0164: 1 and S0390: 1.	AR052: 3, AR096: 3, AR053: 2, AR089: 2, AR033: 2, AR039: 1, AR060: 1, AR104: 1, AR055: 1, AR061: 0 L0439: 2, L0747: 2, L0756: 2, H0556: 1, S0116: 1, H0333: 1, H0427: 1, H0156: 1, L0646: 1, L0657: 1, L0384: 1, L0543: 1, H0670: 1, H0521: 1, H0478: 1, L0745: 1, L0749: 1, L0757: 1 and L0591: 1.	AR033: 8, AR060: 6,
	Asp-39 to Gln-44.	Pro-37 to Cys-42, Pro-52 to Gly-63.	Ile-35 to Ser-44.
	1679	1680	1681
	149 - 763	29 - 340	24 - 401
	274	275	276
	780819	781376	781623
	HSLJK83	HADFW62	HDTBV64
	264	265	266

VO 01/90304									1	PCT/	US01	1/1645
17								,				
AR089: 3, AR096: 3, AR052: 2, AR053: 2, AR061: 1, AR104: 1, AR055: 0, AR039: 0 L0752: 8, L0766: 6, S0444: 5 1 10770: 5 1 10439:	5, L0731: 5, S0360: 3, H0031: 3, L0803: 3, S0126: 3, L0755: 3, L0758: 3,	S0358: 2, H0722: 2, H0090: 2, H0056: 2, L0805: 2, L0665: 2	2, H0519: 2, S0330: 2, H0521: 2, L0747: 2, H0170:	1, H0716: 1, H0740: 1, S0114: 1, S0212: 1, S0442:	1, S0354: 1, H0580: 1, H0329: 1, H0431: 1, H0497:	1, H0331: 1, H0574: 1, H0632: 1. H0486: 1. H0427:	1, L0021: 1, H0036: 1, H0274: 1, S0010: 1, H0318:	l, H0581: 1, H0374: 1,	10052: 1, H0596: 1, H0597: l, H0545: 1, H0373: 1,	S0388: 1, H0107: 1, S0003:	H0622: 1, H0553: 1, H0163:	1, H0087: 1, T0067: 1, H0494: 1, H0560: 1, S0438:
AR089: AR052: AR061: AR055: L0752: S0444: 5	5, L073 H0031: 3, L075	S0358: 2, H005	2, H051 H0521:	1, H071 S0114:	1, S035 H0329:	1, H033 H0632:	1, L002 H0274:	1, HOS8	H0052: 1, H054	S0388:	H0622:	1, H008 H0494

WO 01/90304		PC 1/USU1/104
	55-78, 31- 48	207-223
1, S0440: 1, S0426: 1, UNKWN: 1, L0598: 1, L0763: 1, L0769: 1, L0638: 1, L0761: 1, L0641: 1, L0776: 1, L0379: 1, L0657: 1, L0809: 1, L0519: 1, L0791: 1, L0663: 1, H0684: 1, H0672: 1, S0378: 1, H0522: 1, S0404: 1, S0406: 1, S0028: 1, L0750: 1, L0756: 1, L0753: 1, S0031: 1, H0445: 1, H0595: 1, S0436: 1, L0581: 1, L0608: 1, S0011: 1, S0026: 1, S0192: 1, S0196: 1, H0423:	AR096: 1, AR052: 1, AR033: 1, AR060: 1, AR089: 1, AR061: 0, AR055: 0, AR053: 0, AR104: 0 H0009: 2, H0583: 1, S0045: 1 and S0250: 1.	AR096: 6, AR053: 6, AR052: 4, AR089: 3, AR060: 2, AR039: 2, AR033: 2, AR055: 2, AR104: 2, AR061: 1 L0740: 8, L0749: 8,
	1682 Met-1 to Gly-7, Pro-99 to Phe-104.	Glu-46 to Asn-51, Gly-56 to Gly-63.
	1682	1683
	225 - 578	119 - 901
	77.7	278
	781821	782028
	HOHBR65	HRABZ84
	267	268

VO 01/90304		PCT/US01/1645
	· · · · · · · · · · · · · · · · · · ·	
0779: 0752: 0774: 0754: 0046:	H0318: 1, H0687: I, H0641: I, L0386: H0519: 1,	0308:
S0040: 4, L0766: 4, L0779: 4, L0471: 3, H0090: 3, H0040: 3, L0748: 3, L0752: 3, S0358: 2, H0644: 2, H0616: 2, L0763: 2, L0774: 2, L0659: 2, L0744: 2, L0774: 2, L0750: 2, L0777: 2, L0758: 2, H0686: 1, H0687: 1, H0583: 1, H0657: 1, H0549: 1, H0586: 1, H0587: 1,	75: 1, H 66: 1, H 66: 1, H 64: 1, H 64: 1, H 64: 1, H 65: 1, L 65: 1, L 73: 1, H 73: 1, H 73: 1, H 73: 1, H	3756: 1, S 55: 1, S 3362: 1, S 26: 1, Si
S0040: 4, L0766: 4, L0779: 4, L0471: 3, H0090: 3, H0040: 3, L0748: 3, L0752: 3, S0358: 2, H0644: 2, H0616: 2, L0763: 2, L0774: 2, L0659: 2, L0769: 2, L0750: 2, L0777: 2, L0758: 2, H0686: 1, H0685: 1, H0657: 1, H0662: 1, S0360: 1, S0046: 1, L0717: 1, H0583: 1, H0651: 1, H0587: 1, H0662: 1, S0360: 1, S0046: 1, H0589: 1, H0589: 1, H0587: 1, H0513: 1, S0280: 1, H0587: 1, H0013: 1, S0280: 1,	H0156: 1, H0575: 1, H0318: 1, H0231: 1, H0266: 1, H0687: 1, S0003: 1, S0214: 1, H0063: 1, H0264: 1, H0641: 1, S0002: 1, S0426: 1, L0764: 1, L0662: 1, L0662: 1, L0663: 1, H0519: 1, H0593: 1, H0365: 1, L0746: 1, L0438: 1, H0519: 1, H0593: 1, H0365: 1, L0746:	1, L0747: 1, L0756: 1, L0780: 1, L0755: 1, S0308: 1, L0591: 1, L0362: 1, L0366: 1, S0026: 1, S0192: 1 and H0506: 1.
S0040: 4, L047 H0040: 3, S035 1, S035 2, L065 2, L075 1, H058: 1, L071 1, L071 1, H0549: 1, H001	H0156: 1, H028: S6028: 1, S000 H0063: 1, S000 L0764: 1, L077 H0555:	1, L074 L0780: 1, L059 L0366: 1 and E
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VO 01/90304 PCT/US01/16450				
45-61				
,				
AR052: 5, AR053: 3, AR096: 2, AR089: 1, AR033: 1, AR055: 1, AR104: 1, AR060: 1, AR061: 1, AR039: 0 L0439: 5, L0770: 4, L0794: 4, L0758: 4, L0665: 3, H0657: 2, S0360: 2, H0039: 2, H0040: 2, H0551: 2, L0803: 2, L0747: 2, L0777: 2, H0423: 2, H0638: 1, S0420: 1, S0007: 1, H0050: 1, H0510: 1, H0594: 1, S0003: 1, H0564: 1, H04994: 1, H0560: 1, H0625:				
Met-1 to Arg-7, Pro-9 to Ile-17, Glu-26 to Tyr-38.				
1685				
231 - 1040				
280				
783017				
HUFAJ06				
270				

142	5 %
123-142	300-316, 176-192
	72 74 75 72 740:
AR052: 51, AR033: 42 AR055: 40, AR053: 36 AR089: 30, AR060: 14 AR061: 12, AR096: 11 AR039: 10, AR104: 6	AR033: 3, AR052: 3, AR089: 3, AR060: 3, AR053: 2, AR096: 2, AR055: 1, AR039: 1, AR104: 1, AR039: 1, L0766: 12, H0659: 5, L0749: 5, S0410: 4, S0422: 4, H0650: 3, H0341: 3, H0032: 3, H0529: 3, L0646: 3, H0520: 3, H0547: 3, H0521: 3, L0748: 3, H0423: 3, H0657: 2, S0280: 2, H0266: 2, H0090: 2, H0040: 2, L0803: 2, L0804: 2, L0666: 2, H0658: 2, H0672: 2, L0756: 2, L0757: 2,
87.	Glu-26 to Gly-33, Glu-44 to Cys-49, Glu-75 to Lys-80. Glu-75 to Lys-80.
1686	1687
77 - 667	139 -
281	282
783316	783318
HDQFV46	нмекн64
271	272
	HDQFV46 783316 281 77 - 667 1686 His-13 to Gln-20, AR052: 51, AR033: 42, Gly-27 to Ser-55, AR055: 40, AR053: 36, Glu-175 to Gly-187. AR089: 30, AR060: 14, AR061: 12, AR096: 11, AR061: 12, AR096: 11,

O 01/90304	PC 1/USU1/10450
	43-67, 17- 34
	·
·	
L0759: 2, S0424: 2, H0170: 1, H0556: 1, H0656: 1, S0401: 1, S0420: 1, S0444: 1, H0728: 1, S0444: 1, H0728: 1, S0446: 1, H0728: 1, S0444: 1, H0728: 1, S0444: 1, H0728: 1, H0318: 1, H0596: 1, H0560: 1, H0647: 1, L0520: 1, L0774: 1, L0521: 1, L0774: 1, L0521: 1, L0774: 1, L0655: 1, L0774: 1, L0655: 1, L0778: 1, L0655: 1, L0778: 1, H0619: 1, H0435: 1, H0670: 1, H0619: 1, H0435: 1, L0750: 1, L0777: 1, L0752: 1, L0775: 1, L0775: 1, L0775: 1, L0775: 1, L0775: 1, H0555: 1, L0775: 1, H0555: 1, L0775: 1, L0752: 1, L0775: 1, H0542: 1 and H0422: 1.	AR039: 10, AR055: 8, AR033: 7, AR053: 7, AR089: 6, AR052: 6, AR096: 5, AR060: 5, AR104: 5, AR061: 4 H0618: 3, H0052: 2, H0411: 1, H0333: 1, H0253: 1, H0622: 1, H0424: 1,
	Gln-77 to Ala-82, Thr-90 to Asp-100, Leu-108 to Ala-120.
	1688
	51 - 413
	283
	783631
	HTLEE85
	273

WO 01/90304		PC1/USU1/16
170-186, 120-136	67-89, 91- 107	40-62, 19- 35
S0378: 1, L0749: 1 and S0436: 1. AR104: 12, AR096: 11, AR055: 10, AR052: 9, AR060: 8, AR061: 5, AR039: 7, AR061: 5, AR039: 5, H0038: 5, H0616: 5, L0758: 5, S0003: 3, L0741: 3, S0278: 2, H0156: 2, H0484: 1, H0638: 1, S0045: 1, S0046: 1, H0638: 1, L0794: 1, S0122: 1 and L0749: 1.	AR055: 8, AR052: 7, AR089: 6, AR060: 6, AR096: 5, AR033: 5, AR104: 5, AR053: 4, AR039: 4, AR061: 4 H0615: 4 and H0556: 1.	AR104: 240, AR061: 184, AR060: 129, AR033: 121, AR089: 99, AR053: 77, AR052: 76, AR055: 67, AR039: 62, AR096: 56 S0136: 8, L0754: 5, L0758: 5, L0768: 3, L0766:
Gly-10 to Arg-18, Leu-23 to Lys-30, Gly-53 to Pro-60, Asn-72 to Arg-81, Ser-86 to Lys-95, Glu-97 to Asp-105.		Thr-37 to Ser-43, Pro-62 to Asn-67, His-73 to Tyr-82, Pro-94 to Ser-102.
1689	1690	1691
73 - 795	29 - 382	1035 - 1340
284	285	286
783713	783883	783892
HCE4Q82	275 HODEC95	HCBBA47
274	275	276

WO 01/90304	PCT/US01/16450
	517-533, 476-492
	223900, 253800, 253800
-	9q31.2
3, L0803: 3, L0749: 3, H0506: 3, H0560: 2, L0598: 2, L0662: 2, L0794: 2, L0804: 2, L0747: 2, L0755: 2, L0685: 2, H0580: 1, R0222: 1, H0642: 1, T0023: 1, H0587: 1, H0268: 1, R0421: 1, S0388: 1, H0268: 1, H0573: 1, L0652: 1, L0652: 1, L0652: 1, L0664: 1, L0652: 1, L0664: 1, L0667: 1, L0772: 1, L0667: 1, L0664: 1, L0667: 1, L0772: 1, L0667: 1, L0664: 1, L0667: 1, L0672: 1, H0519: 1, S0126: 1, H0672: 1, H0519: 1, S0126: 1, L0746: 1, L0759: 1, L0746: 1, L0759: 1, L0746: 1, L0759: 1, L0746: 1, L0759: 1, L0749: 1, L0601: 1, L0603: 1, S0196: 1, H0543: 1, H05443: 1, H05444444444444444444444444444444444444	AR052: 26, AR033: 26, AR053: 18, AR089: 15, AR060: 9, AR096: 9, AR055: 8, AR104: 6, AR061: 5, AR039: 4 H0266: 4, H0547: 4, H0521: 3, L0748: 3, S0358:
	Met-1 to Lys-6, Ser-31 to Ala-45, Cys-102 to Glu-107, Arg-151 to Asp-157, Glu-215 to Leu-220, Ser-264 to Leu-270,
	1692
	2247
	287
	783939
	нѕкво61
	277